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Extrapolation of the Evidence on Teratogenicity of Chemicals Between Humans and Experimental Animals: Chemicals Other Than Drugs

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Epidemiologic literature regarding the possible association between malformations and 23 exposures or occupations other than pharmaceutical products, was analysed. The qualitative level of scientific evidence was classified into four categories: high (ethanol, methylmercury, PCBs, laboratory work), limited (anesthetic gases, carbon monoxide), low (hexachlorophene, LSD, nitrous oxide, smelter work, tobacco), and inadequate (all other exposures). Human data for exposures belonging to categories "high" and "limited" were quantitatively compared to results of animal teratogenicity tests of the relevant chemicals. Ethanol, methylmercury, and PCBs have caused malformations in experimental animals, and the effective doses have ranged from 0.2 to 8.0 times the effective human doses. Ethanol and PCBs caused similar types of lesions in some animal species as have been observed in humans.

Key words: chemical exposures, malformations, epidemiology, teratogenicity testing, ethanol, methylmercury, PCBs

FOREWORD

This review was commissioned to the authors by the Advisory Subgroup in Toxicology of the European Medical Research Councils in 1981. The need was felt for a consideration, a posteriori, of the current practice of testing chemicals for teratogenicity and other embryotoxic effects in laboratory animals. This practice is based upon the belief that results of such tests will predict the ability (or lack of ability) of specific chemicals to induce similar effects in man.

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The aim of the review was to assess the correspondence between epidemiological and experimental observations. The rationale was that an analysis restricted to those chemicals for which human data are available would allow an estimation of the proportion of false positive and false negative results in experimental tests.

It was soon apparent that this approach had several limitations:

1) The demonstration of lack of effects in man requires an amount and quality of epidemiological evidence which are very difficult to attain: Therefore, the identification of chemicals giving false positive findings in laboratory animals is problematic.

2) Reports of an association between exposures and embryotoxic effects in man are not equally convincing for the existence of a causal link. In fact, studies have covered a wide range of objectives, from hypothesis generation to hypothesis confirmation. Therefore, the epidemiological literature had to be thoroughly scrutinized in order to identify those chemicals for which an effect on man could be considered as firmly established. In addition, in many studies observations could lead to more than one interpretation, so that a description was needed of the essential findings in each study. The criteria and the interpretation by the authors are stated.

3) Epidemiological observations (of any quality) regarding teratogenicity following chemical exposures which have been reported in the scientific literature are very numerous. It was therefore decided to exclude medicaments from the first phase of the exercise.

4) The review was restricted to structural malformations for two reasons. Inclusion in the epidemiological review of studies of other embryotoxic effects would have further increased the size of the review. In addition, the majority of analytical epidemiological studies (ie, those allowing for the recognition of cause-to-effect relationships) are of the case-control type, in which only one effect is taken into consideration.

The original objective thus turned out to be too ambitious. The review does not allow conclusions to be drawn about the usefulness of teratogenicity testing in terms of public health (ie, assessment of the predictivity of the results of tests in laboratory animals). However, it has two elements of interest. On the one hand, it provides a thorough analysis of epidemiological findings with explicit evaluations of their reliability. In addition, it pinpoints some established (or almost established) causal associations with teratogenicity in the human species, which require investigation of their mechanism of action.

No conclusion can be drawn on the validity of the practice of testing chemicals for teratogenicity. The many different types of embryotoxicity and the variation of doses and responses in different mammalian species reinforces the view of the Advisory Subgroup in Toxicology that only an increase in knowledge of the mechanism of action of embryotoxins will lead to sound methods for the prediction of this hazard of human exposure.

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INTRODUCTION

Tests for teratogenicity and other embryotoxic effects in experimental animals are commonly used in the belief that they predict risks in humans. Yet, the validity of this approach has not been established; animals species vary considerably in their susceptibility to teratogenic agents [1]. In principle, experimental and epidemiological data should be systematically compared so as to enable the identification—if any—of "false positive" and "false negative" chemicals in experimental tests and thus to estimate the sensitivity and specificity of these. In fact, for only a limited number of environmental chemicals is information on their effects on the human fetus available, and the validity of this information requires a thorough scrutiny. In addition, because of the intrinsic limitations of the epidemiological approach, the identification of "true negatives" is questionable. An alternative, albeit reductive, approach is the identification of "true positives" and the qualitative and quantitative comparison of epidemiological and experimental data concerning these. Thus, the present review has two purposes: 1) to evaluate whether chemicals with evidence of teratogenicity in humans show, on a qualitative ground, similar effects in animals, and 2) to evaluate whether human and animal effective doses are comparable. A similar although qualitative approach regarding carcinogenicity of chemicals turned out to be rewarding [2,3], since it revealed that almost all human carcinogens are carcinogenic in experimental animals also (although quantitative comparability is still uncertain).

The exercise required a preliminary evaluation of the epidemiological findings regarding the effects of specific exposures on the human fetus. In view of the relatively large number of exposures for which some epidemiological studies or observations on man were available and required scrutiny, some limitations have been introduced: 1) The present review does not consider therapeutic agents; 2) only epidemiological studies regarding congenital anomaly (eg, structural malformations and neurological defects) as an end point are considered (thus excluding birth weight alterations, abortions, still births, and behavioral effects). Yet in experimental studies all expressions of teratogenicity and embryotoxicity detected during pregnancy or at birth are recorded. The limitation of epidemiological data to congenital anomalies is technical rather than scientific; it is realized, however, that in terms of public health, ie, for predicting effects in humans, all embryotoxic effects should be considered [1,4].

METHODS

Chemical exposures, other than drugs, for which there are human data on teratogenicity have been identified through Medline and Toxline data banks using key words such as teratogenicity, malformations, and birth defects. Additional sources of literature were some reviews [1,5,6], and files maintained by the authors. No new articles were included after the summer of 1982. The chemical exposures identified from the literature are reported in Table I. It is obvious that for complex exposures and some mixtures comparison with animal data is problematic.

The following criteria have been adopted in the evaluation of epidemiologic evidence for each chemical or exposure: A *high level* of evidence was achieved when information on malformations and exposures was reliable (ie, derived from objective sources), and 1) analytical (ie, controlled) studies were available and no positive bias

TABLE I. Chemicals (Other Than Drugs) for Which Epidemiologic Data Have Been Evaluated

Individual chemicals	Mixtures, complex exposures
Carbon monoxide	Anesthetic gases
Fluoride (water fluoridation)	Coffee
Halothane	Ethanol
Hexachlorophene	Gasoline
LSD	Cannabis
Lead	PCBs (Kanechlor)
Methylmercury	Potato blight
Nitrous oxide	Smelting work
2,3,5-T[a]	Soft water
TCDD	Laboratory work (solvents)
Vinyl chloride	Spray adhesives
	Tobacco

[a]Contaminated by TCDD and other dioxins.

was identifiable (ie, systematic errors in selection of subjects, collection of information, or comparability of groups); no positive confounder was identifiable (ie, a factor which was predictive of the occurrence of the disease and was associated with the exposure being investigated); the association was strong (say, relative risk greater than two) or, if not strong, it was substantiated in two or more studies; the results were unlikely to be due to chance alone; ie, the statistical power of the study seemed to be sufficient as to detect the reported association; given the purpose of the review, we are not concerned with a low power as a cause of "false negative" results; in addition, several independent studies done under different circumstances make the cause-effect relationship more likely; or alternatively, 2) several case reports showed association between a very rare exposure and a very rare malformation.

Limited evidence was achieved when several case reports or uncontrolled clinical series were available; analytical studies were available and biases, if present, were unlikely to explain all of the reported association, and the association was weak and not shown to be reproducible.

A *low level* of evidence was based on the following: few case reports or clinical studies, geographic and/or chronological correlation studies only, individual analytical studies showing a weak and biased and/or confounded association.

Inadequate evidence was based on studies showing serious bias or serious confounding or on insufficient available information.

These criteria are only to be considered as guidelines to make the comparison with animal data easier. The categories of high, limited, low, and inadequate level of evidence do not indicate a different teratogenic potency of chemicals but different qualitative levels of available knowledge.

The following criteria were applied while the original literature was reviewed:

1) Regardless of the terms used for the frequency of malformations in the original papers, we use the term *prevalence* rate (number of malformed children per 100 live births or deliveries).

2) The literature search considered only maternal exposure during pregnancy. Thus, maternal exposure before conception and paternal exposure were not considered.

3) With some exceptions, individual case reports and geographic or historical correlation studies have been mentioned but not discussed in detail. Case reports may

reflect fortuitous observations, since defective children can be more easily reported than normal babies from mothers exposed to a chemical. Geographic correlation studies usually do not allow for the identification of the effect of the relevant agent separately from that of other exposures.

4) The design of some studies (eg, on anesthetic gases) is unusual in epidemiology, since they are based on a cross-sectional selection of (exposed and unexposed) groups at the time of the study, and a retrospective ascertainment of pregnancy outcomes and previous exposures; they are reported as "exposure-selective retrospective studies" [7].

5) Consideration of the potential confounding factors in studies on malformations is limited. It is reasonable to think that at least maternal age, parity, and socioeconomic status may be potential confounders [8], since they predict the occurrence of at least some malformations and are associated with many exposures. Also, alcohol consumption could confound association measures in some studies.

EPIDEMIOLOGIC STUDIES

Anesthetic Gases

Available analytical studies are summarised in Table II. These studies have been defined as "exposure selective studies" [7] since they were based on cross-sectional selection of exposed and unexposed groups from professional or employment records or similar files. In general, groups were subsequently refined according to the information obtained in questionnaires.

Exposure data were collected in most of the studies through mail questionnaires. Exceptions were the studies of Cohen et al [9], who directly interviewed nurses but not other groups, and of Ericson & Källén [10] who used hospital records for ascertaining duration of exposure. In most studies, exposure was characterised by duration and period of pregnancy. In two studies, duration and levels of exposure to halothane were respectively scored by the interviewed subjects [11,12]. Cohen et al [13] report malformations of the offspring of chairside assistants exposed to nitrous oxide alone and to mixtures containing nitrous oxide. Lauwerys et al [14] collected information on the different types of anesthetic gases to which physicians and nurses were exposed.

Pregnancy outcome was identified through mail questionnaires in all studies but ones in which use was made of a national delivery register [10].

Response rates ranged from 40 to 92%, with 70% as a common value. Among those studies reporting the response rate separately for exposed and control subjects, in two the rate was lower for the unexposed group.

Results. Considering only females exposed at least in early pregnancy, the studies of Knill-Jones et al [15], Corbett et al [16], Cohen et al [17], Knill-Jones et al [18] (only when a 1:1 matching of unexposed to exposed subjects was introduced), Göthe and Hoffman [19] (only when nonsmokers were considered), Pharoah et al [20] (only for heart-great vessels defects) and Cohen et al [13] (only for light users of anesthetics) showed statistically significant differences of prevalence rates between exposed and unexposed subjects. Of these studies, four controlled for potential confounders. Rate ratios can be calculated from these studies and ranged from 1.6 to 3.6 [18] (however, when 1:2 matching was introduced, the rate ratio became 1.1, not

TABLE II. Epidemiologic Evidence on Teratogenicity of Anesthetic Gases[a]

Author(s) and year	Country	Type of study	Subjects and sample size	Source(s) of information—exposure[a]	Source(s) of information—outcome	Prevalence rates of defects at birth (per live births or pregnancies)	Comments[b]
Askrog and Harvald, 1970 [151]	Denmark	Retrospective exposure-selective study	578 Nurses of anesthetic dept. + 174 anesthetists (respondents: 72%)		Mail questionnaires	Wives of male anesthetists: 3/137; female anesthetists: 0/26; anesthetists nurses: 1/229	
Cohen et al. 1971 [9]	U.S.A.	Retrospective exposure-selective study	159 Nurses, 50 female anesthetists, 81 physicians (controls) (respondents: 77% of anesthetists and physicians)	Interviews to nurses, mail questionnaires to other groups	Interviews to nurses, mail questionnaires to other groups	Female anesthetists 2%; physicians 4.2%	
Knill-Jones et al. 1972 [15]	U.K.	Retrospective exposure-selective study	1241 Women anesthetists + 1678 women general physicians (controls) (respondents: exposed 82%, unexposed 80%	Mail questionnaire (all trimesters)	Mail questionnaire	46/893 (5.2%) among exposed; 89/1835 (4.9%) among controls Exposed in I-II trimesters: 6.5%; unexposed in I-II trimester: 2.5%	$p < 0.2$
Rosenberg and Kirves, 1973 [11]	Finland	Retrospective exposure-selective study	300 Married nurses (58 in anesthesiology) (respondents: 70%-75%)	Mail questionnaire (duration and level of exposure to halothane scored)	Mail questionnaire	No malformations observed	Exposure to halothane

Corbett et al, 1974 [16]	U.S.A.	Retrospective exposure-selective study	621 Nurse anesthetists (respondents: 85%)	Mail questionnaire	Mail questionnaire	16.4% Among nurses practicing during pregnancy; 5.7% among nurses not practicing during pregnancy	$p < 0.05$ Hemangiomas: 12 in the exposed group vs. 1 in the unexposed inguinal hernias: 14 vs. 2
Cohen et al, 1974 [17]	U.S.A.	Retrospective exposure-selective study	All operating room personnel in U.S.A. (49,585) + 23,911 pediatricians and nurses (controls) (respondents: 41-76%)	Mail questionnaire (I trimester and 1 year before conception)	Mail questionnaire (title emphasizes health risks of anesthetics)	Exposed females: 9.6%; unexposed females: 5.9%; wives of male anesthetists: 5.4%; wives of male pediatricians: 4.2%	$p = 0.001$ $p < 0.04$ *Conf. control*
Knill-Jones et al, 1975 [18]	U.K.	Retrospective exposure-selective study	7,949 Male anesthetists (under 65) and controls (general doctors and anesthetists not working in first trimester of their wives' pregnancies) (respondents: 70%)	Mail questionnaire on male and female exposure (I trimester)	Mail questionnaire	4.5% In children of exposed males; 5.5% in children of exposed females; 3.6% in children of unexposed doctors When *matching* for potential confounders: e.m. 4.5%; unexposed males 3.2%; e.f. 5.5%; unexposed females 1.5% 5.3% e.f.; 4.9% u.f.	Minor defects: e.m. 3.09%; e.f. 3.19%; u.d. 2.35% a = $p < 0.02$ *Conf. control* $p < 0.01$—minor defects 3.1% vs. 2.1% $p < 0.01$—*1:1 matching* p. value n.s.—*1:2 matching*

(continued)

TABLE II. Epidemiologic Evidence on Teratogenicity of Anesthetic Gases* (Continued)

Author(s) and year	Country	Type of study	Subjects and sample size	Source(s) of information—exposure[a]	Source(s) of information—outcome	Prevalence rates of defects at birth (per live births or pregnancies)	Comments[b]
Cohen et al, 1975 [21]	U.S.A.	Retrospective exposure - selective study	2,798 Male oral surgeons + 4,797 male dentists (exposed: subjects having worked at least 3 hours /week with anesthetists the year before their wives' pregnancy) (respondents: 39–65%)	Mail questionnaire	Mail questionnaire (title emphasizes health effects of anesthetics)	4.7% in the exposed group; 4.1% in the unexposed group	p = 0.26 *Conf. control*
Tomlin, 1976 [152]	U.K.	Case report				Three malformed children from "approximately" 50 anesthetists	Types of defects not reported
Spence et al, 1977 [153]	U.K. and U.S.A.	Retrospective exposure-selective study	Combined analysis of Cohen (1974) and Knill-Jones (1972, 1975) studies	Mail questionnaire (only exposure in early pregnancy considered) (response rate in U.S. male controls: 45%)	Mail questionnaire	5.5% In female anesthetists 4.0% In female controls 5.0% In male anesthetists 3.7% In male controls	p < 0.04 p < 0.01 (Greatest difference in U.S. data = low response rate)
Göthe and Hoffman, 1977 [19]	Sweden	Retrospective exposure-selective study	All Swedish male anesthetists and female anesthetist nurses vs. internal physicians and surgical nurses; index group: 1,382 pregnancies; control group: 2,002 pregnancies (response rate: 89.7%)	Mail questionnaire	Mail questionnaire	Male anesthetists: 1.7% among exposed 1.8% among unexposed female nurses: 3.0% exposed 3.2% unexposed 5.9% exposed 2.9% unexposed	*Conf. control* smokers nonsmokers—p < 0.01

Pharoah et al, 1977 [20]	U.K.	Retrospective exposure-selective study	7992 Women physicians (respondents: 72%)	Mail questionnaire	Mail questionnaire	Anesthetists: heart-great vessels 13.8%*, talipes 5.2%*; other physicians: heart-great vessels 3.6%*, talipes 1.7%*; National Child Develop. *Study*: heart-great vessels 6.6%* talipes 4.1%*	* = $p < 0.05$
Rosenberg and Vänttinen, 1978 [12]	Finland	Exposure-selective study	212 Anesthetists + 356 Pediatricians (response rates: 85% and 64%	Mail questionnaire (subjective score of halothane vapours)	Mail questionnaire	29/248 Pregnancies (11.6%) among anesthetists 28/266 pregnancies (10.5%) among pediatricians	Six luxations of hip and 3 inguinal hernias in anesthetists, vs. none in the controls; but 2 vs. 11 "other defects"
Tomlin, 1978 [154]	U.K.	Uncontrolled exposure-selective study	75 Anesthetists with 135 children			Five musculoskeletal or nervous system defects among 135 children of approximately 75 anesthetists	Ependymoma included as a malform
Ericson and Källén, 1979 [10]	Sweden	Exposure-selective study	669 Female operating room personnel, vs. all women employed in medical work	Hospital records (duration of exposure in pregnancy)	Computerized delivery records (1973 and 1975)	22 Observed defects vs. 26 expected (from 986 children in the exposed group and 19,127 in the unexposed)	*Conf. control*

(continued)

TABLE II. Epidemiologic Evidence on Teratogenicity of Anesthetic Gases* (Continued)

Author(s) and year	Country	Type of study	Subjects and sample size	Source(s) of information—exposure[a]	Source(s) of information—outcome	Prevalence rates of defects at birth (per live births or pregnancies)	Comments[b]
Tomlin, 1979 [22]	U.K.	Retrospective exposure-selective study	340 Anesthetists: "exposed" were those spending at least 1/2 of their work time in anesthetic practice (respondents 92.4%)	Mail questionnaire	Mail questionnaire	9.3% For exposed in the last 20 years; 7.2% for exposed before; 4.3% for unexposed (children of male and female anesthetists not separately analysed)	Excess due to CNS and musculoskeletal defects Henoch-Schönlein purpura, muscular dystrophy and diabetes included as malformations
Cohen et al, 1980 [13]	U.S.A.	Retrospective exposure-selective study	107,771 Dentists 150,000 chairside assistants (response rates: 70 and 75%)	Mail questionnaire (nonusers of anesthetics, light users (=1–8 hours/week), heavy users (=more than 8 h/wk) in the same year and the year before concept)	Mail questionnaire	Wives of male dentists: nonusers 4.9%, light users 4.6%, heavy users 4.8%. Female chairside assistants: nonusers 3.6%[a], light users 5.7%[a], heavy users 5.2%. (nitrous oxide alone exposure = 5.5%)	*Conf. control*
						Exposed chairside assistants: 2.47%; unexposed c.a.: 1.15%	a = $p < 0.02$
							musculoskeletal defects—$p < 0.01$

Lauwerys et al., 1981 [14]	Belgium	Retrospective exposure-selective study	121 Male and 28 female anaesthetists + 63 male and 176 female operating theatre nurses vs. 62 + 27 dermatologists, 290 + 22 occupational physicians, 14+33 intensive care nurses, 20 female social nurses and 168 other doctors and nurses; Response rate: 47%, ranging from 41.5% (intensive care nurses) to 55.5% (social nurses)	Mail questionnaire (duration of exposure, hours/day of exposure, types of anaesthetics, ventilation system)	Mail questionnaire	Exposure of mothers in pregnancy: full-term malformed 7/259 pregnancies; premature malformed 3/259; still-births, malformed 0/259. Never-exposed mothers: full-term malformed 47/1,519 pregnancies; premature malformed 5/1,519; still-births, malformed 3/1519	Type of anaesthetics was ascertained. No differences among groups for smoking habits and drug consumption. No difference among groups for birth defects was statistically significant

*e.m., exposed males; e.f., exposed females; u.m., unexposed males; u.f., unexposed females; n.s., not significant.

[a]Level and trimester of exposure in brackets.

[b]Comments include: p-values, types of malformations, specific exposures, serious identifiable bias, and confounding—when confounding factors were controlled in the study this is reported as *Conf. control*.

statistically significant) or 3.8 (only for heart-great vessels defects) [20]. Other studies [9,11,14,19,21, limited to smokers] showed either no or not statistically significant differences. The negative result obtained by Ericson and Källen [10] is particularly relevant, since outcome was assesed through an objective source.

Types of malformations. Excesses of specific malformations were shown by Corbett et al [16, haemangiomas and inguinal hernias], Knill-Jones et al [18, minor defects], Pharoah et al [20, heart-great vessels defects], Rosenberg & Vänttinen [12, luxation of hip and inguinal hernias], Tomlin [22, CNS and musculoskeletal defects] and Cohen et al [13, musculoskeletal defects].

Minor malformations are more prone to information bias [23], ie, an apparent excess may be due to more accurate reporting by the exposed subjects. This is particularly suggested when unexposed controls show an excess of unspecified "other" defects [12]. In addition, ependymoma, Henoch-Schönlein purpura, muscular dystrophy, diabetes, heart murmur, and malabsorption syndrome were included among malformations in single studies.

In some studies, the purpose of the investigation was mentioned in the questionnaire title ("health effects of anesthetics"); this may have induced more accurate answers by the exposed groups.

Evaluation of anesthetic gases. Due to the aforementioned shortcomings (inconsistency of results, nonobjective sources of information, possible recall bias), the available evidence of teratogenicity of anesthetic gases is *limited*. Nitrous oxide has been associated with an excess of birth defects among female chairside assistants in one study only [13] (see Table II), and the evidence of teratogenicity is *low* for it. The evidence for *halothane* is *inadequate*.

Caffeine (Coffee)

Ingestion of caffeine, mainly from coffee, tea, and cola beverages averages at 190 mg/d per adult population in the US [24]. Five epidemiologic studies on the association between coffee and caffeine consumption during pregnancy and malformations in the offspring have been reported and are reviewed below; results are summarized in Table III. Also, other types of reproductive effects have been studied [25].

In the prospective Boston Collaborative Perinatal Project, over 50,000 pregnant women were interviewed on their consumption of drugs [26]. Over 5,000 women reported use of caffeine, usually as an ingredient in medication. No specific type of malformation was related to caffeine intake. Yet, coffee drinking was not controlled for and the authors recommend caution in interpretation of results.

In a case-control study reported by Borlée and co-workers [27], the parents of 202 case children and of 175 control children were interviewed on the types of beverages consumed. Proportions of mothers drinking more than 8 cups of coffee per day were 23% among cases and 13% among controls ($p < 0.05$). The association did not involve specific types of malformations. The frequent coffee drinkers appeared to be older than the women drinking less coffee.

TABLE III. Epidemiologic Evidence on Teratogenicity of Coffee Consumption*

Information on coffee consumption	Sample size	Malformations	Risk ratio (consumers vs. nonconsumers)	Significance (p)	Reference
Prospective I	50,300 Births	All	~ 1 (Use of caffeine medication)	–	Heinonen et al. 1977 [26]
Retrospective I	190 Cases	All	1.5 (≥ 8 Cups/day)	$p < 0.05$	Borlee et al. 1978 [27]
Retrospective I	2,030 Cases	380 Inguinal hernia, 299 cleft lip ± palate, 277 cardiac, 194 pyloric stenosis, 120 cleft palate, 101 CNS (1)	Pyloric stenosis: 1.8 (≥ 200 mg caffeine/day)	95% c.l.: 0.8-3.9	Rosenberg et al. 1982 [28]
Retrospective I	12,205 Women	All	~ 1.0	–	Linn et al. 1982 [29]
Retrospective I	482 Cases	83 CNS, 150 skeleton, 95 cardiovascular, 154 oral clefts	~ 1.0	-	Kurppa et al. 1982 [30]

*I, interview; Q, mail questionnaire; (1), for each group of defects, 712 other malformations were used as a comparison group.

In a case-control study, 380 infants with inguinal hernia, 299 with cleft lip with or without cleft palate (CL ± CP), 277 with cardiac defects, 194 with pyloric stenosis, 120 with isolated cleft palate, and 101 with neural tube defects were compared with 712 other malformed infants (control group). Maternal ingestion during pregnancy of tea, coffee, and cola was investigated through personal interviews. Relative risks ranged up to 1.8 (0.8–3.9) for pyloric stenosis (total daily caffeine intake greater than 200 mg vs. no ingestion). The corresponding estimates for inguinal hernia, CL ± CP, cardiac defect, cleft palate, and neural tube defect were 1.4, 1.3, 1.5, 0.8, and 0.8, respectively. None of the point estimates of relative risks was significantly greater than unity and no dose-response relationship was apparent [28] (Table III).

Linn and co-workers [29] carried out a retrospective study on 14,500 women, among which compliance was 90%. There was no association between malformations in the offspring and coffee consumption even in the highest exposure category (> 4 cups of coffee per day). Finally, the mothers of 482 children with central nervous system, skeletal, cardiovascular, and oral cleft malformations from the Finnish Register of Congenital Malformations were interviewed and compared to referent mothers of healthy children. No difference was found in the consumption of coffee [30].

The evidence on the teratogenicity of coffee or caffeine intake is *low*. The one study reporting an effect does not rule out the results of other negative studies.

Carbon Monoxide

At least eight cases of documented maternal intoxication from coal gas used for illumination were associated with retarded mental or psychomotor development in the offspring [4,31,32]. In three of these cases autopsies were performed and showed softening of basal ganglia, cerebral atrophy, hydrocephalus, and microcephalus [32]. In nine other case reports [4], various types of brain pathology, including damage of the basal ganglia and microcephaly, were detected. The evidence is *limited* for a direct effect of carbon monoxide in inducing structural changes of the CNS in the offspring of exposed women.

Ethanol

Previous reviews indicated a causative role of alcohol in the "fetal alcohol syndrome, FAS" [33,34] (Table IV). The features of this syndrome are not unequivocal [35–37]; Sokol [38] has proposed that a reliable diagnosis should include at least one typical feature of each of three groups of defects: growth retardation, CNS effects, and facial characteristics. The presence of FAS in live born children in France, Sweden, and the US ranged between 1/600 and 1/1000 [37,39a,b,40]; it doubled when milder syndromes were included. Prevalence rates of 19% were reported among children born from mothers consuming 56 or more grams alcohol daily [37]; elsewhere, rates were in the order of 35% in children of chronic alcoholics [40,41]. In these studies, the quantity of alcohol consumption was estimated by interview and was probably subject to a reporting bias.

In three series of FAS children the prevalence of microcephaly, oral clefts, and heart defects were respectively 40–90%, 1–25%, and 25–50% [42–44], ie, greatly in excess of the corresponding rates in the general population. When considering the studies including information about alcohol consumption and the presence of major structural malformations, the association is less clear. In a prospective study, there was an increase in the frequency of major malformations (32 vs. 9% in the control group) in the offspring of heavy drinkers consuming a mean daily dose of 2.2 g alcohol/kg [45]. Microcephaly was the main type of malformation noted, and it explained most of the difference between the groups. Hypospadias and genito-urinary and oral malformations were more common in infants of alcohol abusers as compared to the controls [39a,b]. No excess oral clefts and cardiovascular defects have been noted in a study of Tennes and Blackard [46].

– There is a *high* evidence of a teratogenic effect of alcoholism in humans in so far as it induces FAS. A causal relationship between maternal alcohol consumption and other structural malformations in the offspring is less well established.

Gasoline

Mental retardation, scaphocephaly, prominent occiput, poor head growth, and minor anomalies were found in two children whose mothers reported inhalation of gasoline. Four children with a similar syndrome occurred in 1973–77 in Shamattarere, Canada, but gasoline sniffing could not be ascertained [47]. The evidence is *inadequate*.

Hexachlorophene

Halling [48] compared the occurrence of malformations in six groups of nurses using 1% hexachlorophene soap and in six hospital-matched groups not using the

soap. Pregnancy outcomes were retrieved from the records of obstetric departments; the source of the exposure data was not stated. Exposure consisted of 20-60 washings per day, both before and during the first trimester of pregnancy. Loss to follow-up was 15% in three hospitals. Major malformations were 0/233 live births of the controls (vs. 4–5 expected) and 25/460 live births of exposed women. There was no adjustment for age and parity, but it is unlikely that confounding could explain such a difference.

Baltzar et al [49] reported two studies. In the first study, 63 hospitals were asked to provide lists of women in medical occupations who had left work because of childbirth in 1965–75. Only 31 hospitals replied and provided data on approximately 1,500 women. All women had worked at least in the later part of pregnancy. Malformed children were identified through the Swedish Register of Congenital Malformations in 1965–72, and from the Medical Birth Record Register (MBRR) thereafter. Results are given separately for the 1965–72 period (5 malformed children born from 930 women, vs. 9–10 expected), and for the 1973–75 period. In 1973–75, observations are reported separately for 200 women from three hospitals in the Gothenburg area and for 260 women from other hospitals. Observed and expected malformations were respectively 13 vs. 4 in the former group and 3 vs. 5 in the latter (this observation of an excess in the Gothenburg area could not be referred to any particular exposure).

The second study reported by Baltzar et al [49] describes the outcome of 29,806 pregnancies among women employed in medical occupations in 1973–75. These women, identified from a register of medical personnel, were linked with the birth register through the personal identification number. Malformations were collected through the Medical Birth Record Register. Expected numbers were calculated from all deliveries in Sweden in 1973–75 (323,011 infants). A total of 1,551 defective children were born in the study group, vs. 1,491 expected; an excess in Gothenburg was confirmed (42 observed, 29 expected; $p < 0.01$). A comparison between the use of hexachlorophene soaps in "periods presenting possibilities for exposure during pregnancy" and malformations in the offspring revealed no apparent association.

Some aspects in these two studies reported by Baltzar et al require comments: exposure was ill-defined; in the first study only 31/63 hospitals responded, and the quality of information from these hospitals was probably different; there was no information on individual exposures to hexachlorophene. There is a *low level* of evidence about hexachlorophene teratogenicity in man.

Lead

The data on the teratogenicity of lead to humans are historical and cannot be evaluated critically [50]. A case report on the association of lead intake in moonshine whiskey and fetal anomalies has been published, but it may also be a result of alcohol intake [51]. No epidemiological evidence is available to evaluate the possible teratogenicity of lead to humans.

LSD and Cannabis

Several case reports have been published regarding children born to mothers taking LSD during or before pregnancy [52–55]. Most of them describe similar skeletal defects; a common feature was distal agenesis of limbs. In these reports the LSD doses were not estimated, but it is stated that they were sufficient for psychedelic

TABLE IV. *Epidemiological Evidence on Teratogenicity of Ethanol (Alcoholic Beverages)*[a]

Information on exposure	Sample size	Malformations	Exposure level	Risk ratio and statistical significance	Reference
Retrospective, I	127 Cases from alcoholic mothers	Facial characteristics, growth deficiency, psychomotor disturbances	—	—	Lemoine et al. 1967 [35]
Retrospective, I (clinical observations)	11 Cases with "fetal alcohol syndrome" (FAS)	Short palpebral fissures (11), microcephaly (10), maxillary hypoplasia (7), limb anomalies (8), altered palmar crease pattern (8), cardiac anomalies (7)	—	—	Jones and Smith, 1975 and 1973 [33,36]
Prospective, I	23 Chronic alcoholic women + 46 matched controls	6 Babies with FAS in the alcoholic group (including short palpebral fissures, ptosis, strabismus, joint anomalies)	—	—	Jones et al. 1976 [41]
Retrospective, I (clinical observations)	6800 Births	Babies with FAS	—	Severe cases 1/1000, less severe 1/400	Dehaene et al. 1977 [39a]
Prospective, I	633 Women	"No specific pattern of anomalies"	Nondrinkers: 326 women (I), ⩽45 ml absolute alcohol daily: 249 (II), > 45 ml daily average (absolute alcohol): 58 (III)	9% Congenital anomalies in Group I 11% in Group II 32% in Group III ($p < 0.001$)	Ouellette et al. 1977 [45]
Prospective, I	70 Infants born from "alcoholic" mothers + 93 "control" infants	A *priori definition* of "features compatible with FAS"	"Alcoholic" mothers: one ounce or more of absolute alcohol/day or 5 + drinks on occasion	9/70 Infants with FAS from heavy drinkers (⩾1.0 ounces/day) 0/31 from moderate drinkers (0.1-0.9) 2/62 in control infants	Hanson et al. 1978 [37]

Retrospective for 2 infants, prospective for the other 2: I	4 Dead infants	Different features of brain malformation at neuropathology	"Heavy ethanol intake" in pregnancy (2 women) + occasional "binge" (2 women)	—	Clarren et al. 1978 [42]
Prospective, I	23 Pregnancies, 21 live births	FAS and other anomalies	"alcohol problem"	7/21 FAS, other 7/21 thought to have alcohol-related problems	Olegard et al. 1979 [40]
Retrospective	204 Abusers 11,923 controls	All	Alcohol abuse was defined "clinically"	FAS (2.5% in abusers vs. 0% in control), hypospadias, genito-urinary and oral malformations increased	Sokol et al. 1980 [39b]
Prospective, Q	278 Births	All	5 Exposure categories during I and III trimester	No excess risk	Tennes and Blackard, 1980 [46]
Retrospective	109 Infants with FAS	All	—	Anomalies in FAS infants: microcephalus (84%), various facial anomalies (11–74%)	Majewski, 1981 [44]
Retrospective	71 Infants with FAS	All	—	Anomalies in FAS infants: microcephalus (44%), various facial anomalies (7–68%)	Nestler et al. 1981 [43]

*I, Interview; q, questionnaire; FAS, fetal alcohol syndrome.

effects. LSD was either taken throughout pregnancy or in the first trimester. In at least three reports, there were multiple exposures (cannabis, drugs, or other strong hallucinogens).

A further report [56] describes a baby with multiple malformations, including absence of phalanges, born to a mother who had taken 3 doses 9 months prior to conception. Finally, another report describes the birth of a normal baby from a woman who had been a high-level consumer up to 2 months before pregnancy [57].

No malformations were described in a follow-up study on ten pregnant women with an intake of LSD which entailed hallucinatory phenomena [58]. All women took LSD in the first trimester of pregnancy and some also later.

Another uncontrolled follow-up study [59] included 247/300 women taking LSD and other drugs and responding to a questionnaire: during follow-up 148 of them had pregnancies (120 live births) and 14 malformations were detected, including six turned-in feet, two tibial rotations, and one unspecified bone deformity of legs. No birth defect was observed among the 12 women taking LSD during pregnancy.

The median single dose for mothers of malformed babies was 100 μg (range 75–250 μg).

Overall, the level of evidence for LSD is *low* since the positive findings derive from case reports, most of which describe multiple drug intake. However, the evidence cannot be entirely disregarded, because distal limb agenesis, which has been described in the offspring of six mothers taking LSD, is otherwise observed rarely.

The epidemiologic literature on teratogenic effects of cannabis is scanty and overlaps with that on LSD. In two case reports [53,54], the mothers of babies with distal defects of limbs consumed both cannabis and LSD. In a further report [56] and in one follow-up study [59] concerning mainly LSD, cannabis is mentioned as one of several drugs concurrently consumed by the mothers. The level of evidence for cannabis is *inadequate*.

Methylmercury

Knowledge on the embryotoxicity of methylmercury derived from studies regarding the ingestion of contaminated food [reviews by Koos and Longo, 60, Chang et al, 61]. These studies include the well-known epidemic in Minamata, Japan [62]. In the latter population severe neurological disorders in adults ingesting methylmercury-contaminated fish were described as early as in 1953. However, only a few years later children affected by symptoms resembling those of cerebral palsy were described. Between 1953 and 1971 at least 25 children were born with brain damage. After systematic research, a syndrome could be observed and this was also connected to alkylmercury ingested in contaminated fish by the mothers.

A comparable epidemic of microcephaly and other neurological disorders took place in Iraq in 1972, as a result of ingestion of grain treated with methylmercury [63,64]. Out of 32 infants exposed in utero, ten showed cerebral palsy at the age of 1 year. In Iraq as well as in Minamata, mercury was found in biological samples from the affected mothers and children. A dose-response relationship has been established [65]. A total maternal exposure to 1–1.2 mg/kg corresponded to a 50% frequency of neurological signs in the offspring [65]. In Iraq the total ingested doses were about 150 mg and the daily exposures about 80 μg/kg, with large variations. Observations from Minamata and Iraq have also been confirmed in other small series of cases from

U.S.S.R., Sweden, and the U.S. [60,61,66]. Neuropathology of prenatal intoxication revealed the following in two cases from Matsumoto et al [67] and in two cases from Choi et al [68]: narrowing of gyri, hypoplasia of the basal ganglia and cerebellum, and heterotopic neurons in cerebral and cerebellar white matter.

Methylmercury can be considered a teratogen with a *high* level of evidence, taking into account the morphologically detectable changes in the CNS.

Kanechlor (PCBs)

A "PCB-induced fetopathy" (Yusho) has been described as a feature of an episode of intoxication occurring in 1968 in Japan, in which approximately 1,000 persons of different ages were accidentally intoxicated by rice oil contaminated with Kanechlor 400, a technical tetrachlorobiphenyl product. The Yusho oil contained about 1,000 ppm of PCBs and 5 ppm of polychlorinated dibenzofurans [69]. The etiologic role of the ingestion of this oil was ascertained for intoxicated persons through the following: 1) examination of oil containers, shipping records of the producing company, and records of oil dealers; 2) analysis of biological samples; 3) a case-control study on 121 adult patients and 121 adult controls concerning use of oil and fats [70].

A fetotoxic effect of Kanechlor was first recognised when a group pf intoxicated mothers delivered 13 babies with a syndrome which included dark brown pigmentation of the skin and mucous membranes, retardation of growth, gingival hyperplasia, spotted calcification of the skull [70-72]. Hyperkeratosis, atrophy of the skin, and cystic dilatation of hair follicles were described in stillborn babies delivered by exposed mothers [70,71]. PCBs were detected in the skin by chromatography.

One, five, and one females had been exposed respectively in the first, second, and third trimester only, two had been exposed throughout pregnancy, and the time of exposure was unknown for four. Miller [71] estimated an average exposure of 11 weeks. Intake was estimated to be 65-839 μg PCB/kg/day [73].

There is a *high* level of evidence that the contaminants found in the food oil are human teratogens. Whether PCBs, dibenzofurans, or possibly dioxins were the causative agents cannot be resolved.

Potato Blight

Renwick [74,75] reported a positive geographic correlation between potato blight and anencephaly-spina bifida (ASB). Subsequently to this, a number of geographical and temporal correlation studies have been undertaken; by and large they failed to confirm Renwick's *findings* [76-85].

Lorber et al [86] reported two cases of ASB born to mothers on a potato-avoidance diet during pregnancy.

A few analytical studies are available. Robert et al [87] interviewed mothers of 336 malformed babies (neural tube defects) and as many normal controls in Glamorghan, South Wales. Cases and controls were born in 1964-66 and their mothers were approached through a questionnaire several years later. One-third of both cases and controls did not reply or were not traced. Home-grown potato consumption did not differ among cases and controls.

In another case-control study on potato consumption in pregnancy [88], 83 children with spina bifida, collected retrospectively up to 12 years before the study, were compared with 85 children chosen from the general population and matched to

the cases by sex, month, and year of birth, residence and social class. Mothers were interviewed by health visitors. No difference in maternal potato consumption during pregnancy was found between cases and controls. Potential confounders like maternal age and parity were not considered. In this study, a negative confounding may have been introduced by strictly matching for residence and date of birth, since blighted potato consumption varies according to social class, place, and time.

In another case-control study in New York City [89], 265 mothers of babies with ASB diagnosed in 1970–72 and 549 control mothers agreed to be interviewed by telephone on their current potato consumption. Controls (2 per case) were chosen from birth certificate files and were matched to cases by parental residence and date of birth. No relative risks were reported, but they can be computed from the published figures. Most of them are lower than one. The study, however, had some shortcomings: cases represented 70% of those who were eligible for interview, whereas the corresponding proportion for controls was 94%. In addition, although nonrespondent controls were replaced, the matched controls were not always dropped when the case refused the interview. Thus, a comparison bias (higher social class selection of respondent cases) cannot be excluded. Finally, the analysis did not take into account maternal age and parity. However, bias and confounding so strong as to mask a positive association are unlikely.

Nevin and Merrett [90] reported on 88 pregnant women who had a previous infant with ASB and who were advised to avoid eating potatoes in subsequent pregnancies. The advice was followed by 27 women who were compared with the other 61. ASB occurred respectively in 2/27 (8.7%) and in 2/61 (3.6%) ($p > 0.05$). This study leaves some open questions: The 88 women derived from a larger group but mechanisms of selection are not stated; inclusion of women in the groups (potato-free or not) was not random and confounding cannot be ruled out; numbers are small.

The available studies do not indicate a role of potato blight in the etiology of ASB. Correlation studies were negative. Analytical studies concern potato (and not specifically blighted potato) consumption or avoidance; none of them suggested any association with ASB. Shortcomings in the design of these studies cast some doubt on the acceptability of such negative results but do not provide any suggestion of a positive association.

Smelter Work

In a recent study [91], a list of women employed as copper smelters in a company in 1955–1976 was compared with the records of pregnancies of the local hospital. The completeness of either company records or follow-up is not discussed. Malformations were 17/291 among the offspring of women in the smelter as compared to 22/1,000 in controls ($p < 0.005$). Multiple malformations contributed to this difference. Sulphur dioxide, lead, arsenic, and cadmium have been suggested as the possible causative agents [92,93]. The results were not controlled for possible confounding factors. This individual study provides a low level of evidence on the teratogenic hazards of copper smelting.

Soft Water

Fedrick [94] reported a negative correlation between water hardness and prevalence rates of anencephaly in ten areas in the U.K. This contrasts with a similar correlation study [95] in Liverpool and south-west Lancashire where the highest

incidence rate of anencephalus (3.9/1,000/year) was found in a "hard water" area, and the lowest rate (2.9/1,000/year) in a "soft water" area.

Lowe et al [96] correlated water hardness with a) CNS malformations (mortality data) in 48 South Wales areas and b) anencephaly in 58 country boroughs in England and Wales. Correlation coefficients were all negative. Analogously, negative correlation coefficients were found by Crawford et al [97] comparing water hardness and anencephaly mortality in 58 English large towns (many comparisons were made and most correlation coefficients were statistically significant). Morton et al [98] carried out similar work in South Wales considering CNS malformations. The correlation coefficients were negative but low and statistical significance was weak ($p < 0.05$). Multiple comparisons were made.

A case-control investigation in Cardiff included 108 cases of neural tube defects and as many controls matched for sex, age, and social class. Determination of 11 elements in the drinking water yielded similar results for cases and controls [99].

Another case-control study in Canada included 468 deaths from anencephalus and a random sample of 4,129 live births [100]. Mothers lived in 142 localities for which the water concentration of 14 elements was available. No association was found for any of the 14 elements. Risk estimates were adjusted for potential confounding factors (parity, season and year of birth, maternal age, and others). However, samples were not collected from case and control dwellings.

Overall, these studies provide *inadequate* evidence on the teratogenicity of soft water.

Laboratory Work (Solvents)

Five studies suggest an association with teratogenicity (Table V).

Kucera [101] reported that five out of nine mothers of infants with sacral agenesis had been exposed to miscellaneous industrial solvents, as ascertained retrospectively. No control group was used. Other malformations were not analysed.

A Swedish group has published three studies on laboratory personnel possibly exposed to solvents for whom other exposures have not been ruled out. Meirik et al [102] identified from the university files the laboratory staff who had been working during pregnancy. They had given birth to a total of 245 newborn children. Malformations were recognised both through interviews and from the Swedish Malformation Register. Eleven children with serious malformations were found vs. four expected on the basis of the rates among deliveries in the same hospital birth wards, adjusting for maternal age and parity. The 11 malformations included four anal or oesophageal atresias or stenosis, and two children with pes equino-varus.

The second study was similar in design but regarded offspring of women working in chemical laboratories of the pharmaceutical industry [103]. In the exposed group, prevalence of major malformations was 6/106 (5.8%) vs. 2/297 (0.7%) in the referent group. The malformations included two oral clefts and one multiple gut atresia. The exposed-referent comparison was uncontrolled for the potential confounding factors. It is reported, however, that the age distribution was similar in the two groups.

The third study was similarly designed and covered laboratory workers of pulp and paper industry. Major malformations were 6 vs. 2.9 expected, standardized for age, parity, and hospital [104]. Malformations included two gut atresias, two heart defects, one anencephaly, and one cleft palate.

TABLE V. Epidemiologic Evidence on Teratogenicity of Laboratory Work*

Information on exposure	Sample size	Malformations	Risk ratio and significance (p)	Reference
Retrospective Q	9 Cases	Sacral agenesis	5 Mothers exposed to organic solvents	Kucera, 1960 [101]
Retrospective (University files + interview)	322 Women	All	4 Cases of anal or oesophageal atresia in women working vs. none in women not working in a laboratory during pregnancy	Meirik et al. 1979 [102]
Retrospective I, Q	405 Women	All	6 Major malformations out of 103 infants among "chemical laboratory workers" vs. 2/297 among the nonchemical workers. One multiple gut atresia in the former group	Hansson et al. 1980 [103]
Retrospective, Q	890 Women	All	6 Major malformations (vs. 2.9 expected) among women working in laboratories (2 gut atresia)	Blomqvist et al. 1981 [104]
Retrospective, I	120 Cases	CNS defects	RR = 6.5 ($p<0.01$) for exposure to organic solvents	Holmberg, 1979; Holmberg and Nurminen [105,106]

*I, interview; Q, mail questionnaire.

In the three studies, ascertainment of both employment and malformation data were reliable. Even though small numbers of malformations could be collected in each study, the combined studies provide strong evidence for an excess of oral clefts and gastro-intestinal atresias over the rest of the population. The studies were not designed in order to identify the causal factors. These are thought to be various solvents by the authors.

A Finnish case-control study has identified exposures to various organic solvents to be overpresented (14 vs. 3) among the case-mothers as compared to the control-mothers from the same maternity welfare district [105,106]. An excess of exposure to dusts was also reported. The study included 120 nervous system malformations reported to the Finnish Register of Congenital Malformations and a similar number of controls. Information on exposures was collected retrospectively in a personal interview.

The evidence on the teratogenicity associated with certain types of laboratory work is *high*. The evidence for solvents being the causal factor remains unestablished.

Spray Adhesives

Of the two studies reported, one is in abstract and gives insufficient information [107]. The other study reports use of spray adhesives more often in the homes of cases as compared to those of controls; it is limited because of very low returns in the postal interview [108]. Only 22% (N = 56) of the initial pairs could be subjected to analysis. Thus the evidence on teratogenic effects of spray adhesives is *inadequate*. The chemical composition of spray adhesives needs to be clarified.

2,4,5-T and TCDD

It is not possible to analyse separately exposure to dioxins from exposure to other chlorinated chemicals (such as 2,4,5-T) contaminated with dioxins. However, an effort has been made to specify for each study the agent to which people were mainly exposed.

Case reports and informal investigations. This section is mainly based on the review by Young et al [109]. Tung et al [110] described four pregnant women who had been hit by herbicide sprays in Vietnam: two mothers had children with Down's syndrome. Other anecdotical reports about Vietnam have been published by Rose and Rose [111] and Honoroff [112]. A survey was conducted by a Committee of the U.S. National Academy of Science [113] in three Saigon hospitals, but the material was considered inadequate, and no conclusions could be reached.

Roan and Morgan [114] carried out an epidemiologic study based on the hospital records in the areas near Globe, Arizona, where 2,4,5-T had been massively sprayed. Analytical measurements in tissues and fluids were all negative, and allegedly no trends in reproductive mortality and morbidity could be attributed to herbicide use. Two cases of malformations in human infants were described in Lapland and attributed to phenoxy herbicide spraying [115].

In New Zealand, a report by Sare and Forbes [116] described two babies with spina bifida, born to mothers having been exposed to 2,4,5-T spraying during pregnancy. The degree of exposure was not known, and in one case exposure occurred

after the neural tube closed [these comments were made by a subcommittee of the N.Z. Agricultural Chemicals Board: 117].

Geographic pathology studies. Cutting et al [118] surveyed retrospectively malformations occurring in 22 hospitals in South Vietnam, as reported on the daily summaries prepared by midwives. Private clinics were not surveyed, some hospital records had been destroyed, home deliveries were excluded, as was the Chinese group of the population. Prevalence rates were 5.5/1,000 in 1960–65 (period of light spraying of Agent Orange) and 4.5/1,000 in 1966–69 (heavy spraying). Overall, 2,355 defects in 488,852 births were identified. Anencephaly, cleft lip/palate, club-foot, and hydrocephaly accounted for 80% of all malformations. There was no nonexposed category and only a dose-response relationship could be measured. It has also been pointed out [109] that heavily sprayed areas were underrepresented and there was no precise knowledge of exposure of pregnant women.

Two geographic pathology studies on 2,4,5-T spraying in New Zealand have been reported. McQueen et al [119] collected cases of anencephaly and spina bifida in three areas where clusters of cases were allegedly present. Cases were collected in 1974–76 from hospital records, and a comparison was made between observed and expected numbers in each area. In Northland there were seven cases, which correspond to the expected value. Five cases occurred in Taranaki, of which three were in the same street. In Waikato there were eight cases (one anencephaly, seven spina bifida), all diagnosed in 1 month. The mothers were interviewed about 2,4,5-T contacts in pregnancy: 3/7 mothers of cases in Northland, 3/4 mothers of cases in Taranaki (one is excluded because she conceived elsewhere) and possibly 4/8 mothers of cases in Waikato declared to have conceived during the period of 2,4,5-T use. However, the authors state that only in one or two cases was there "some exposure" to 2,4,5-T in the critical period, and they concluded that there is no evidence. This is not to be considered an analytical study, since it lacks controls and standardized interviews.

Hanify et al [120] compared prevalence rates of malformations in seven New Zealand areas in 1960–66 (when no exposure to 2,4,5-T occurred) and in 1972–76 (when 2,4,5-T spraying was common). Quantity, dates, and places of spraying were collected from the companies. No geographic or temporal correlation could be found, with the possible exceptions of talipes and hypospadias + epispadias (no mention is made of the changing attitudes in the registration of birth defects).

Other correlation studies relating to 2,4,5-T spraying in agriculture have been reported in Australia [121], Arkansas [122], and Hungary [123]. These studies concentrated respectively on anencephaly and meningomyelocele in 1965–76, cleft lip/palate in 1943–74 and cleft lip/palate, cystic kidney, anencephaly, and spina bifida in 1970–76. They were all negative. A further study of geographic and time correlations in Western Australia suggested a role of "insecticides" and "herbicides" in the occurrence of cleft lip/palate, but no firm conclusion could be reached [124].

A Birth Defect Registry has been established as a surveillance system in the Seveso area, which was highly polluted by 2,3,7,8-TCDD in 1976 [125]. It collects malformations (all types) in 11 towns (222,000 residents) from the lists of live and still-births: this is followed by home visits of paediatricians. From 1978 to 1980,

newborns contacted increased from 86 to 94%. The Registry area was divided into four zones: A, B, R, and Out (allegedly not polluted) depending on the TCDD concentrations in the soil. Rates were compared with Lombardy hospital records and other birth defect registries. High rate ratios (RRs) were found, in comparison with Lombardy hospital records, for spina bifida (RR = 2, $p = 0.1$) and hypospadias (RR = 13.5, $p < 0.0001$). In addition, the RR for "other anomalies" in the zone A + B vs. R + Out was 6.6. These preliminary results must be interpreted cautiously: an excess of hypospadia and "other anomalies" in the A + B zones could result from a detection bias due to greater diagnostic accuracy and reporting in highly polluted areas.

Analytical studies. The only available studies concern paternal exposures. Smith et al [126] published a preliminary report of reproductive outcomes among male pesticide applicators using 2,4,5-T in New Zealand. They were postally interviewed about exposure, whereas pregnancy outcomes were obtained from their wives. Twenty-four malformations (2.0%) were found in children of the exposed group, and 18 (1.6%) in children of the unexposed group. The RR was 1.25 (90% c.i. 0.8–2.0). Four heart defects were found in the exposed group, vs. 1 among the unexposed. In a further paper [127], these data are reanalysed, dividing the exposed group into men who were not spraying during their wives' pregnancies, those who sprayed chemicals other than 2,4,5-T, and those who sprayed 2,4,5-T during the pregnancy: The rates of congenital defects were respectively 9/401 births, 9/113 births, and 13/486 births (the differences were not statistically significant).

Townsend et al [128] described a cohort study on wives of 930 employees of Dow Chemical (Michigan Division), working at least 1 month in 1939–75 in chlorophenol processes. These were considered "potentially" exposed to dioxins. The same number of men working at least 1 month in the same plant with no chlorophenol exposure formed the control group. The compliance rates were low (62–63%). For all congenital malformations, the crude and age-adjusted rate ratios were 0.96 and 0.85, respectively, when exposure to any dioxin was considered. Ratios were 1.18 and 1.08 when exposure to TCDD alone was considered. This study does not report observations separately for an unspecified number of workers developing chloracne following an accident in 1963.

The available analytical studies on 2,4,5-T and TCDD refer only to paternal exposures. Evidence of teratogenicity of maternal exposure is *inadequate*.

Tobacco

The possible teratogenicity of cigarette smoking has been investigated in several well-designed studies as reviewed by Landesman-Dwyer and Emanuel [129] and Johnston [130]. The designs and results of recent studies are summarised in Table VI. Fedrick et al [131] reported an increase in congenital heart defects among smokers in material based on 17,000 pregnancies of the British Perinatal Mortality Survey. The findings were not confirmed by several other studies [26,132–135]. In some studies a small effect (less than 1.5-fold) was observed [136]. In some investigations, heavy smoking was associated with the occurrence of central nervous system (CNS) malformations [26,133,134] but the effect has been considered modest at most. In some

TABLE VI. Effect of Smoking During Pregnancy on the Malformations in the Offspring: Epidemiologic Evidence*

Information on smoking	Sample size	Malformations	No. cigarettes smoked	Risk ratio smoker/non-smoker	Significance (p)	Reference
Retrospective Q	16,200 Births	All	>1/d	<1	No	Underwood et al., 1965 [155]
Retrospective I	16,000 Births	Heart	>1/d	1.5	<0.001	Fedrick et al, 1971 [131]
Retrospective I	18,600 Births	All	>1/d	1.2	No	Andrews and McGarry, 1972 [137]
		Oral clefts		2	<0.05	
Prospective?	14,600 Births	Heart		~1	No	Yerushalmy 1973 [132]
Prospective I	50,300 Births	All	>1/d	<1	No	Heinonen et al. 1977 [26]
Retrospective I	1,400 Cases	All	>1/d	1.1	No	Kelsey et al. 1978 [133]
			>20/d	1.6	<0.05	
Retrospective Q	10,500 Births	All	>1/d	~1.5	<0.05	Himmelberger et al, 1978 [136]
Prospective I	66 Cases	Oral clefts	>1/d	1.7	<0.01	Ericson et al. 1979 [138]
	66 Cases	CNS	>1/d	~1		
Retrospective I	69,000 Births	All	>1/d	~1	No	Evans et al. 1979 [134]
		Anencephalia	>20/d	1.8	<0.5	
Prospective I	14,700 Births	All	>1/d	~1	No	Christianson, 1980 [135]
		All	>20/d	1.2	<0.05	
Retrospective I	320 Cases	CNS	≥1/d	~1	No	Hemminki et al. 1983 [139]
	420 Cases	Oral clefts	≥1/d	1.3	No	
	520 Cases	Musculo-skeletal	≥1/d	1.3	No	

*I, interview, Q, mailed questionnaire

studies an association between maternal smoking and oral clefts has been observed [133,137,138], but again this has not been confirmed [26,134,139].

Taken together, the literature on the effects of maternal smoking on congenital malformations in the offspring fails to show any consistent strong effect. The modest association seen in several studies between heavy smoking (> 20 cigarettes/d) and central nervous system malformations may show a weak effect or confounding. The designs of the positive studies have not been superior to those of the negative studies. The evidence is *low*.

Vinyl Chloride

Infante [140] analysed birth certificates in 1970–73 in a group of Ohio communities, three of which had at least one vinyl chloride polymerisation plant in operation. Prevalence rates of birth defects (per 1,000 live births) were as follows: 10.14 in the entire Ohio state, 17.37 in Ashtabula, 18.10 in Painesvile, and 20.33 in Avon Lake (the three communities with PVC plants). In the three communities, the excess was statistically significant ($p < 0.01$). However, similar prevalence rates were found also in two other cities without PVC plants. A major contribution of CNS defects to the excess was observed in Painesville (with PVC facilities) and in North Ridgeville (without PVC facilities).

On this basis, a case-control study was conducted by Edmonds et al [141] in Painesville. All babies born with CNS malformations in the Painesville hospital in 1970–74 (six with anencephaly and nine with spina bifida) were compared with a group of 30 control babies (the first born immediately before and the first immediately after the case). Parents of the cases were interviewed, whereas information for the controls was collected from the clinical records. None of the 15 case parents and two of the 30 control parents worked in PVC plants; more controls than cases had mothers working within 10 miles from Painesville's PVC plant.

Another case-control study was conducted by Edmonds et al [142] in Kanawha County (West Virginia, U.S.): All but one incident cases of CNS malformations occurring in 1970–74 were compared with a group of control babies identified as in the previous study and matched to the cases by paternal education, maternal age, month of birth, race, and social status. Parents were interviewed by telephone on their work in PVC manufacturing plants and residence place. Two out of 41 fathers of cases and 2/41 fathers of controls worked in PVC plants during the conception time; 0/41 case fathers and 3/41 control fathers worked in PVC plants with a contract work before conception. More cases than controls lived within 3 miles from the PVC facilities ($p < 0.02$) Matching by paternal education (which is strictly associated with job) could have introduced negative confounding. Reviews of the available studies are provided by Wagoner and Infante [143] and Clemmesen [144]. We conclude that the three studies provide *inadequate* evidence of the association between environmental or paternal exposure to vinyl chloride and birth defects in humans.

Water Fluoridation

Mainly, correlation studies are available. Rapaport [145] estimated prevalence rates of Down's syndrome in Illinois towns divided into three categories of levels of water fluoridation and reported a positive correlation. Two other investigations, however, showed absence of such geographic correlations [146,147]. Only Erickson's paper took maternal age into account. In another study [148], prevalence rates of

TABLE VII. Evaluation of Levels of Evidence on Teratogenicity in Humans (According to the Criteria Listed in the Text)

High level	Limited	Low level	Inadequate
Ethanol	Anesthetic gases	Coffee	2,4,5-T
Methylmercury	Carbon monoxide	Hexachlorophene	Fluoridation[a]
PCBs		LSD	Gasoline
(Kanechlor)		Nitrous oxide	Halothane
Laboratory work		Tobacco	Lead
(solvents?)		Smelter work	Potato blight[a]
			Soft water[a]
			Spray adhesives
			Marihuana
			TCDD
			Vinyl chloride

[a]There is some evidence that potato consumption, water fluoridation, and soft water are not associated with human malformations.

Down's syndrome were very similar in 30 towns before fluoridation, in the same towns after fluoridation, and in 321 other communities with levels of fluoride lower than 0.03 ppm. Confounders like maternal age and temporal trends of Down's syndrome were taken into account in the pre-/after-fluoridation comparison. No short-term effect of fluoride on risk of Down's syndrome was apparent (relative risk = 0.95; upper 95% confidence limit 1.2).

A further study dealt with congenital malformation patterns before and after fluoride introduction in Birmingham, U.K. [149]. The minor changes in the prevalence of malformations were attributed to demographic changes or to modified ascertainment and classification. The authors' conclusion is that there was no evidence of an association.

An American study shows prevalence rates of birth defects respectively in cities which had and cities which did not have fluorinated water supplies, and it takes maternal age into account [150]. The result is negative.

Since the design of negative studies is superior to that of the one positive study, there is some evidence that water fluoridation is not a determinant of malformations.

The level of epidemiologic evidence, reviewed above, is summarised in Table VII.

EVALUATION OF EPIDEMIOLOGICAL AND ANIMAL EVIDENCE

Experimental findings regarding compounds with high or limited evidence of teratogenicity in humans (Table VII) have been analyzed and summarized in the Appendix. In the experimental studies, all expressions of embryotoxicity detected during pregnancy or at birth were taken into consideration. Below are compared the experimental and human findings in qualitative and quantitative terms. References to the articles summarized in the Appendix are indicated by A and the number of the reference (A1, A2, etc.).

Oral or injected doses are compared directly between experimental animals and humans. For inhaled doses the calculations assume an inhalation volume of 15 m^3/24

TABLE VIII. Animal Tests on Chemicals With High and Limited Evidence on Teratogenicity in Man After a Quantitated Exposure (for details, see text)

	Human data			Animal data			
Substance	Daily dose (mg/kg)	Risk	Ref.	Species	Daily dose (mg/kg)	Risk	Ref. from Appendix
Carbon monoxide	?	CNS defects	[4,31,32]	Mouse, rat, rabbit	30-250 ppm	Resorptions	A12, A15, A19
Ethanol	2,000	33% (FAS)	[37,40,41]	Mouse	3,000-5,000	~ 30% (FAS-type)	A28, A29
Halothane[a]	60 ppm = 0.6 ml/kg	1.5 times	[9-23,156]	Mouse	1.10 l/kg	Threefold (skeletal)	A1
Methylmercury	1.0[b]	25% microcephaly	[65]	Mouse, rat	5-10	50% Malformations	A40-A47
				Cat	0.25	32% Malformations	A48
Nitrous oxide[c]	3,000 ppm = 0.3 l/kg	5.5 vs. 3.6% 1.5 risk	[13,156]	Rat	300 l/kg	Malformations sixfold	A8,A10
				Rat	0.2 l/kg	Fetal deaths	A9
Polychlorinated biphenyls	0.5[d]	100% (symptoms) 30% (small for date)	[70,71,73]	Monkey	0.10	13% (Skin symptoms) 50% (low birth weight) 40% (lethality)	A59,A60

[a]It is assumed that halothane is the responsible agent in anesthetics; in fact the evidence is inadequate (see Table VII).
[b]For methylmercury 1mg/kg is the total ingested dose; the daily doses were in the order of 80 μg/kg.
[c]It is assumed that nitrous oxide is the responsible agent in anesthetics: in fact the evidence is low (see Table VII).
[d]Estimated intake of Kanechlor.

h by a person of 50 kg by weight (= 0.3 m^3/kg/d). The weights of mice are taken as 20 g and those of rats as 300 g. Oxygen consumption by weight is assumed to be two (rat) and three (mouse) times higher per time unit in rodents than in man. This equals daily inhalation volumes of 0.6 m^3/kg/d for the rat and 0.9 m^3/kg/d for the mouse. Complete absorption of the inhaled compound is assumed in the airways of experimental animals and man.

The quantitative comparisons between epidemiological and animal results are shown in Table VIII.

Anaesthetic Gases, Halothane

Cleft palates and skeletal malformations were induced in mice at a 3 h inhaled dose of 1% halothane [A1]. In one study using a similar dose no effects were seen in rats and rabbits [A6]. Lower doses, about 0.2% halothane, were investigated only in rats exposed by inhalation for 8 or 12 h; fetal deaths and decreased fetal weights were noted [A3–A5]. When these results are translated into an inhaled dose, halothane caused malformations in mice after inhalation of 110 L of 1% halothane/kg, ie 1.10 L of halothane/kg. Rats experienced fetotoxicity and depressed weight gain, when inhaling 300 L of 0.2% of halothane/kg, ie, 0.6 L of halothane/kg.

The limited epidemiological evidence for teratogenicity of occupational exposure in the operating rooms suggested an excess of malformations at different sites in different studies and was not consistently related to skeletal malformations. The halothane concentration in operating rooms ranges between 0.1 and 60 ppm [156]: assuming a breathing volume of 5 m^3 during an 8-h working day, these would correspond to intakes in the order of 0.0005–0.03 L of halothane, ie, 0.01–0.6 ml of halothane/kg. This is several orders of magnitude lower than the effective doses in mice and rats. However, the meaning of this comparison is doubtful, since the contribution of halothane to the teratogenicity of anaesthetic gases—if any—is not demonstrated.

Anesthetic Gases, Nitrous Oxide

Many types of malformations were induced in rats inhaling either 45–50% or 70–75% nitrous oxide for 24 h [A8,A10]. This translates to about 300 L of nitrous oxide/kg. Fetal deaths have been observed at a lower dose of 1,000 ppm inhaled for 8 h [A9]. This translates to 0.2 L of nitrous oxide/kg.

The concentrations of nitrous oxide in operating rooms have ranged between 30 and 3,000 ppm [156]. This would involve inhalation of 0.15–15 L of nitrous oxide in a working day, and a dose of 0.003–0.3 L of nitrous oxide/kg. It can be observed that the upper dose limit is in the range where fetal deaths have been observed in experimental animals. This may be related to the assumed role of nitrous oxide to account for the excess of spontaneous abortions in the female anesthesia staff [9,13,18,22,156].

Carbon Monoxide

Several experimental studies are available indicating embryotoxic effects other than major structural malformations. In mice, 250 ppm of carbon monoxide induced some resorptions and lumbar ribs [A12]. In rats, 150 ppm decreased the physical activity of the pups [A14], 230 ppm decreased weights of the pups [A15], and 30 and 90 ppm caused preimplantation losses [A16]. In rabbits exposed to 90 and 180 ppm, stillbirths were increased and body weights were decreased [A19]; another study with

rabbits was negative [A12]. Fetal deaths and stillbirth were observed in sheep and pigs [A20,A21]. An important corollary to the findings in human. 1–3 h exposure to 1,000–3,000 ppm at near-term caused neurological defects and necrotized areas of brain in 5/9 Rhesus monkeys [A22].

In the case of exposed humans, neurological defects and brain damage have been observed. Unfortunately, no sound data are available on the underlying levels of exposure.

Ethanol

Malformations at differnt organs have been induced in two studies on mice, including, features similar to FAS such as maxillary hypoplasia, oral clefts, microphthalmia, and shortened palpebral fissures [A28,A29]. The doses used were about 3–5 g/kg/d. With the exception of one study mentioning microcephaly, which was inadequately reported [A30], studies on rats have been negative as far as structural malformations are concerned. On the other hand, in teratogenicity tests microcephaly can be easily missed if it not specifically looked for.

Nevertheless, several studies in rats report some form of developmental toxicity such as increased resorptions and reduced weight gain. Alcohol was also reported to induce brain immaturity in guinea pigs [A37], multiple types of malformations in piglets [A38], and oral clefts, absence of kidneys, and kinky tails in dogs [A39]. The study on rabbits was negative in terms of malformations: However, loss of implantation was increased [A26].

The risk of a chronic alcoholist to bear a child with FAS is about 30% (see epidemiologic section). The daily doses consumed by such persons would be above 100 g ethanol, ie, above 1,800 mg/kg/d. This is not too far from effective doses in mice. However, there is a need to emphasize that even though ethanol has been embryotoxic in the rat (at doses of the same order as in mice), malformations and particularly FAS-type anomalies have not been observed in this species. Species other than rats and mice have not been investigated extensively.

Methylmercury

In mice, rats, and hamsters, single doses of less than 10 mg/kg, given at appropriate times, induced structural malformations (mainly oral clefts and cleft palate in mice and heterogeneous malformations in rats and hamsters). No malformations were observed in the miniature swine and dogs at doses which produced toxic effects in the mothers. In some studies, particular attention was given to histological changes in the brain. Cerebellar changes were detected in 8/65 mice given 1 mg/kg/d methylmercury chloride throughout pregnancy vs 0/111 in controls [A43]. In rats, cellular necrosis of the CNS was found following treatments corresponding to maternal liver concentration above 15 μg/g [A49]. In cats, prolonged treatment with 0.08–0.2 mg/kg/d produced dose-related cerebellar histological changes as well as reduced weight at birth [A48].

In rats and mice, daily subcutaneous doses of 5–10 mg/kg or oral doses of 20 mg/kg caused malformations of various types in about half the pups, including cerebellar changes but not microcephaly. The subcutaneous route seems 2–3 times more effective than the oral one. Based on the data from Iraq, Clarkson et al [65] have estimated that a maternal exposure to about 1 mg/kg caused a 50% probability for the child to have CNS effects typical of poisoning, half of which are microce-

phalic. Thus, effective chronic doses in humans seem to be in the same order of magnitude and possibly somewhat lower than effective acute doses in rodents. Both in humans and rodents, histological damage to the CNS has been noted at a 1-mg/kg dose.

PCBs (Kanechlor 400)

PCB compounds have reduced implantations in mice at very low doses of 0.025 mg/kg in one study [A53] and at a dose of 0.5 mg/kg in another [A55]. Up to 50% malformations were seen in mice exposed to 8 and 16 mg/kg of 3,3', 4,4', 5,5'-hexachlorobiphenyl [A56]. Studies on rat and rabbits have not noted malformations [A57] but have observed a decrease in birth weight and an increase in stillbirth at 50–100 mg/kg [A58]. Feeding studies with monkeys at 5 ppm have shown weight reduction in the offspring and some fetal mortality. This corresponds to a dose in the order of 0.1 mg/kg. Thus, PCBs appear to be developmental toxins and cause hyperpigmentation of the skin in monkeys similar to their effect in humans.

In humans, Kanechlor 400 has caused 100% hyperpigmentation symptoms and 30% babies small for date at estimated daily doses of 0.5 mg/kg PCB, the range being 0.06–0.8 mg/kg [70,71,73]. The contribution of dibenzofurans or other contaminants in the Yusho oil cannot be ruled out. Skin changes and low birth weight can be taken as a basis for comparison between effective human and monkey doses. Since 13% monkeys were affected by skin lesions at a dose of 0.1 mg/kg, linear extrapolation would yield 100% response at a dose of 0.8 mg/kg. Thus, the ratio of human/animal dose would be 0.65. This, however, is based on two monkeys. This is a dose range (0.025–0.5 mg/kg) where reduced implantations were observed in mice. Unfortunately, no related observations are available in humans.

CONCLUSIONS

Testing for teratogenicity is required by many national agencies responsible for the safety of food, drugs, and pesticides. Yet a quantitative evaluation of the predictive value of teratogenicity tests had been lacking, although arguments have been presented on qualitative grounds. In the present exercise, a qualitative evaluation was made of the level of evidence of the ability of several chemical exposures to induce malformations in humans. Effective doses and the magnitude of effects were recorded as much as it was possible from the original studies. A number of exposures definitely or plausibly associated to human malformations were so identified. Qualitative and quantitative findings were then compared to observations resulting from animal experiments.

Results are summarized in Table VIII. The accuracy (and therefore the validity) of these comparisons is impaired by several shortcomings: 1) some substances induced different types of lesions in humans and experimental animals, eg, microcephaly induced by methylmercury is only seen in humans; 2) exposure data in humans are often crude; 3) dose-response data in humans (and often in experimental conditions) were largely unsatisfactory, so that comparisons were restricted to the order of magnitude of dose levels giving a similar magnitude of effects; 4) animal studies were by no means consistent, and observations under the most sensitive conditions were used for comparisons.

In the case of ethanol, MeHg, and PCBs, the evidence for a causal association with human malformations was high. These chemicals also induced malformations

under some experimental conditions. However, the experimental effects neither consistently reproduced those observed in humans nor were similar in the different species in which they were investigated. In mice, ethanol produced features similar to FAS as well as other malformations hitherto associated with neither ethanol nor alcoholism in human. No malformations either similar to FAS or of any types were reported in rats or rabbits exposed to ethanol. Had the studies been limited to these two species, the ability of alcohol to induce malformations would have gone unnoticed. However, in the two species, other forms of developmental toxicity would have been apparent.

In humans, methylmercury produced morphological changes in the brain and these were detected also in mice, rats, and cats when appropriate methods were used. On the other hand, other malformations were seen in laboratory animals which would have hardly escaped attention in humans, had they occurred in this species. For PCBs, an experimental counterpart to the changes induced in human fetuses was detected in monkeys only, whereas structural malformations at other sites were found in rodents.

These comparisons should be considered very cautiously. The application of very rigid criteria of analysis of the epidemiological studies has led to the recognition of a very small number of cause-effect relationships. In addition, these conditions referred to malformations which are very rare in people who are not exposed to the relevant agent. On the one hand, at least one experimental counterpart has been identified for the human malformations shown to be associated respectively to ethanol, MeHg, and PCBs and the order of magnitude of the effective doses was not too different in the human and in the experimental conditions.

In addition, malformations at sites different from those described in humans have been seen in laboratory animals given each of the three chemicals. A small part of this difference can be ascribed to the low sensitivity of epidemiological studies in picking up associations. Other reasons may relate to differences in time of exposure and to differences in developmental biology of species.

Finally, one should wonder whether these three chemicals convincingly shown to be human teratogens would have been detected on the basis of conventional routine testing. Had ethanol and PCBs been tested only in rats and rabbits, their ability to induce malformations would have gone undetected. In strict terms, they might be considered as "false negatives." On the other hand, embryotoxic changes in other than structural malformations would have been recognized in the two species. Furthermore, elements treated with agents such as halothane, nitrous oxide, ethanol, and PCBs that caused both malformations and other types of embryotoxicity were more sensitive to the latter than to the former lesions. Carbon monoxide caused no structural malformations but it induced resorptions, stillbirth, and decreased weight gain. On this basis, in pragmatic terms, the practice of considering any experimental embryotoxic effect as a possible predictor of teratogenicity in the human species seems justified.

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APPENDIX A

Experimental studies regarding compounds with high and limited evidence of teratogenicity in humans (Table VIII in preceding section) are summarized below in Tables A-I—A-V. All expressions of embryotoxicity detected during pregnancy or shortly after birth were considered. The results of these tests were used in the previous section, when human and animal data were compared (Table VIII).

(Appendix begins on page 290)

TABLE A-I. Teratological Testing of Anesthetic Gases[a]

Species, exposure, examination	No. of females	Doses used	Survivors/ implants	Malformations/survivors	Other observations (TM = toxic effects in mothers)	Reference
Halothane						
Mice; C-57 BL, inhal. 3 h × 1,	—	0	—	Less than 4/410 (no CP)		Smith et al. 1971 [1]
13 or 14 d, k?, tech. A+E	—	1 and 1.5%	—	24/99 CP + 23/95 limb defects		
Rat: Sprague-Dawley, inhal. 12 h ×	81	0 (air + starvation)	938/992	333/937 with vertebral anomalies + 198/936 with lumbar ribs		Basford and Fink, 1968 [2]
1, 6–10 d, k 20 d, tech. A+E	77	0.8%	913/963	371/911 with vertebral anomalies (142/306 among those treated in days 9–10), 271/884 with lumbar ribs (145/306 among those treated in days 9–10)	TM (anesthetic effect)	
Rat; Sprague-Dawley, inhal. 12 h × 7, 6–12 d, k ?, tech. A		0.2%	—	—	50% fetal death vs. about 10% in referents	Doenicke et al, 1975 [3]
Rat: Sprague-Dawley, inhal. 8 h × 21, 0–21 d, k 21 d, tech. B+E	23	0 (pair-stressed ± pair-fed)	331/341			Pope et al, 1978 [4]
	17	0.16–0.32%	238/246	No increase in malformations	Decrease in fetal weight TM (subanesthetic effects)	
Rat: Sprague-Dawley, inhal. 8h × 21, 0–20 d, k 22 d, tech. A+E	7	0.16%	—	No increase in malformations	Decrease in fetal weight and crown-rump length length	Lansdown et al. 1976 [5]

Rat:CD, inhal. 1 h × 5, 1-5 or 6-10 or 11-15 d, k 20 d, tech. A+E	30	0 (air)	376/408[a]	Not given		Kennedy et al. 1976 [6]
	10	1.4%	123/127[a]	Not given		
	9	1.4%	138/149[a]	Incidence not given (1 fetus with a hematoma)		
	10	1.4%	137/153[a]	Incidence not given— increase in percentage of incompletely ossified or nonossified sternum sections (authors interpret these findings as incidental)		
Rabbit N.Z. Albino. inhal. 1 h × 4?, 6-9 d or 10-14 d or 15-18 d, k 29 d, tech. A+E	9	0 (air)	45/66	Not given		Kennedy et al. 1976 [6]
	9	1.4%	55/74	Not given, but no gross external abnormalities were detected; incidental skeletal findings included incompletely ossified or nonossified sternum sections, supernumerary ribs, and thickened ribs. The incidence of these findings were similar for all groups. One of 46 fetuses from the group treated on days 10-14 showed split and fused sternum sections and incompletely ossified frontal and parietal bones. One of 67 fetuses from the group treated on days 15-18 had an extra sternum section		
	7	1.4%	46/67			
	10	1.4%	67/83			
Halothane + Nitrous Oxide Hamster: *Mesocricetus auratus*, 3 h on day 9, 10 or 11, k 15 d, tech. A+D	91	60% Nitrous oxide, 0.6% halothane	16/109 (Day 11 exposure) 5/112 controls	None detected	Resorptions, fetal weight, crown-rump length decreased	Bussard et al. 1974 [7]

(continued)

TABLE A-1. Teratological Testing of Anesthetic Gases[a] (Continued)

Species, exposure, examination	No. of females	Doses used	Survivors/ implants	Malformations/survivors	Other observations (TM = toxic effects in mothers)	Reference
Nitrous Oxide						
Rat: Sprague-Dawley, 2, 4, 6 days starting day 8, k 20 d, tech. A+E	?	0 45–50%	76/77, 105/147 (all treatment groups)	1/46 Controls had skeletal malformations vs. 57/57 of the treated, mainly defects of vertebral ossification	Resorptions, fetal weight, crown-rump length decreased depending on treatment time; sex-ratio changed	Fink et al. 1967 [8]
Rat, 8 or 24 h × 4–10 d between days 8 to 19 of pregnancy, k 20 d, tech. A	6–12/group	0 ppm, 100 ppm days 10–13, 1,000 ppm days 10–13, 15,000 ppm days 8–13	—	None reported	Fetal death rate increased in several treatment groups	Corbett et al. 1973 [9]
Rat: Sprague-Dawley, inhal. 8 h × 21, 0–21 d, k 21 d, tech. B+E	26	0 (pair-stressed ± pair-fed)	341/354			Pope et al. 1978 [4]
	24	1–50%	309/340	No increase in malformations	Decrease in fetal weight at 10 and 50% nitrous oxide TM (subanesthetic effects)	

Rat: Sprague-Dawley, inhal. 24 h × 1, 9 d, k 20 d, tech. B+E	31	0 (air)	328/343	4/156 examined (1 CNS + eye); skeletal anomalies in 13/170 exam. (including fused ribs)		Lane et al. 1980 [10]
	30	70-75%	286/340	20/138 examined (18 CNS + eye). (In a concurrent group, 1/160 malformations following exposure to anesthetic doses of xenon occurred.) Skeletal anomalies occured in 55/148 examined (including fused ribs).	TM (anesthetic effects)	
Hamster: G.S., inhal. 24 h × 1, 7–11 d, k 15 d, tech. A+E+F	25	0 (0_2 + air)	283/286	0/283		Shah et al. 1979 [11]
	52	70% or 80% in air	579/596	16/579; in total 18 CP, 22 limb defects.		
	52	90% or 95% in air	532/598	28/532; 4 gut herniations		

[a]This proportion refers to a group of females killed at day 14. k, killed; A, visual observation; B, magnified observation; C, dissection; D, razor blade sections on fixed tissue; E, skeletal staining; F, histological examination; G, histochemistry of central nervous system; H, electron microscopy; CL, cleft lip; CP, cleft palate; -- no data.

TABLE A-II. Teratological Testing of Carbon Monoxide

Species, exposure, examination	No. of females	Doses used	Survivors/ implants	Malformations/ survivors	Other observations (TM, toxic effects in mothers)	Reference
Mice: CF-1, inhal. 7 or 24 h d, 6–15 d, k 18 d, tech. A + B + C + E	28	0,	336/364	0/336	Resorptions increased in the 7-h exposure group, lumbar spurs in both exposure groups, decrease in body weight in the 24-h exposure group	Schwetz et al, 1979 [12]
	20	250 ppm (7 h/d),	231/273	1/231		
	17	0,	204/238	1/204		
	18	250 ppm (24 h/d)	198/234	2/198		
Rat, inhal 5–8 min × 10, every other day of pregnancy, tech. A	—	0	—	—	At 15,000 ppm most fetuses resorbed or aborted	Wells, 1933 [14]
		5,900 ppm	—	—		
		15,000 ppm	—	—		
Rat: Long-Evans, inhal. throughout gestation, tech. A	27	0	—	—	Nonsignificant reduction in body weight, low physical activity in pups	Fechter and Annau, 1977 [13]
	26	150 ppm	—	—		
Rat, inhal. from days 2–21, tech. A	18	0	—	—	Decrease in body weight at 24 h postnatally, minor skeletal variants	Hoffman and Campbell, 1977 [15]
	18	230 ppm	—	—		
Rat: Long-Evans, inhal. days 3–20, tech. A		0	—	—	Dose-dependent preimplantation loss, in the 90-ppm exposure only: 38% of pregnancies were successful vs. 100% in the control	Garvey and Longo, 1978 [16]
		30 ppm				
		90 ppm				

Rat: Sprague-Dawley, inhal. 1 h/d throughout gestation, k 20 d, tech. A	17 20	0 500 ppm	— —	— —	Decrease in body weight	Yun, 1978 [17]
Rat: Sprague-Dawley, inhal. 15 min, at day 6 or 7, or at day 13 or 14, tech. A	21 24	~5,000 ppm ~5,000 ppm	— —	— —	Decrease in the body weight	Yun, 1978 [17]
Rat: COBS, inhal. days 4–21, tech. A	— —	0 500 ppm	— —	— —	Decrease in litter	Penney et al, 1980 [18]
Rabbit, inhal. 30 d since mating, tech. A	15 14 17 17	0 90 ppm 0 180 ppm	— — — —	— — — —	Dose-dependent increase in stillbirth and neonatal death, decrease in body weight	Astrup et al, 1972 [19]
Rabbit: New Zealand, 7 or 24 h on days 6–18, k 29 d, tech. A+B+C+E	11 9 12 9	0, 250 ppm (7 h/d), 0, 250 ppm (24 h/d)	77/88 54/54 84/96 54/63	0/77 0/54 0/84 0/54		Schwetz et al 1979 [12]
Sheep, inhal.	—	—	—	—	Fetal deaths when ewes exposed to 100 ppm for 2-3 h	Longo and Hill, 1977 [20]
Pig, inhal.	—	—	—	—	Stillbirth rate from 5% to 17% at 150 ppm	Keller, 1976 [21]
Monkey: Rhesus, inhal. 1-3 h, at near-term, tech. A+F	9	1,000–3,000 ppm	—	—	5/9 newborn had neurological deficits and swollen and necrotic brain areas	Ginsberg and Myers, 1976 [22]

TABLE A-III. Teratological Testing of Ethanol

Species, exposure examination	No. of females	Doses used	Survivors/ implants	Malformations/survivors	Other observations (Tm, toxic effects in mothers	Reference
Ethanol						
Mice: B6D2F$_1$/*J*, i.p. × 1 or × 2, 8-9 d or 10-11 d or 7-12 d, k 18 d, tech. A ± C	43	0 (Solvent) (pair-fed)	393/413	13/393; 7 iris coloboma, 7 others		Kronick, 1976 [23]
	13	0.03 ml/g of 25% ethanol	67/122	14/67: exencephaly in two fetuses; ectrodactyly in the others	TM (hypnotic dose)	
	48	0.03 ml/g of 25% ethanol	321/456	108/321; 74 iris coloboma; 16 ectrodactyly; 5 hypoplastic atria; 6 hydronephrosis; 4 exencephaly; 19 others	TH (hypnotic dose + weight loss)	
Mice: C57BL/6J, diet × 6, 5-10 d, k 19d, tech. A + D	13	0 (Lab. chow + water)	83/90	3/83; 1 eye, 1 heart, 1 abdomen/urogenital		Randall et al 1977 [24]
	16	0 (pair-fed isocal.)	99/105	3/99; 1 skeletal, 2 eye		
	16	?	103/122[a]	31/103 (40 defects); 10 skeletal (syndactyly, adactyly, ectrodactyly, distortion of digits), 3 head, 4 eye, 11 heart, 12 abdomen/ urogenital		
Mice: CBA, diet before conception and throughout pregnancy, k 18 d, tech. A+D+E	10	0 (lab. chow)	47/48	Skeletal: 1/15 examined; soft tissues: 0/32 examined		Chernoff, 1977 [25]
	10	0 (isocal. sucrose)	56/56	Skeletal: 0/18 examined; soft tissues: 0/38 examined		

	10	3 ml/100 (15% EDC)[a]	17/40	Skeletal: 6/6 examined (6 occiput + 3 sternum); soft tissues: 4/11 examined (2 heart + 4 brain = dilated brain ventricles)	
	8	4.3 ml/100 (20% EDC)	12/44	Skeletal: 4/4 examined (4 occiput + 4 sternum); soft tissues: 8/8 examined 7 heart + 2 gastroschisis + 8 eyelids + 8 dilated brain ventricles	
	10[b]	5.7 ml/100 (25% EDC)	14/52	Skeletal: 5/5 examined (5 occiput + 5 sternum); soft tissues: 9/9 examined (8 heart + 1 gastroschisis + 9 eyelids + 9 dilated brain ventricles + 3 exencephaly)	
Mice: C3H, diet before conception and throughout pregnancy, k 18 d, tech. A+D+E	10	0 (lab. chow)	102/110	Skeletal: 2/35 examined (occiput); soft tissues: 0/67	Chernoff, 1977 [25]
	10	0 (isocal. sucrose)	73/73	Skeletal: 1/24 examined (occiput); soft tissues: 1/49 (dilated brain ventricles)	
	10	4.3 ml/100 (20% EDC)	68/68	Skeletal: 18/22 examined (18 occiput + 6 sternum + 5 ribs); soft tissues: 36/46 (36 dilated brain ventricles + 18 heart + 4 exencephaly + 3 gastroschisis)	
	8	5.7 ml/100 (25% EDC)	36/52	Skeletal: 12/12 examined (12 occiput + 5 sternum + 5 ribs); soft tissues: 24/24 examined (24 dilated brain ventricles + 17 heart + 7 exencephaly + 9 gastroschisis)	

(continued)

TABLE A-III. Teratological Testing of Ethanol (Continued)

Species, exposure examination	No. of females	Doses used	Survivors/ implants	Malformations/survivors	Other observations (Tm, toxic effects in mothers	Reference
	10	7.2 ml/100 (30% EDC)	17/61	Skeletal: 6/6 examined (6 occiput + 4 sternum + 6 ribs); soft tissues: 11/11 (11 dilated brain ventricles + 10 heart + 9 exencephaly + 9 gastroschisis)		
Mice: CF-1, diet × 10, 6–15 d, k 18 d, tech. A ±C±E	22	0 (water)	265/274	4/265 (1 brachignathia + CP; 1 enlarged head; 1 clubfoot; 1 with no right subclavian arteria)		Schwetz et al, 1978 [26]
	21	25 ml/kg/d	240/252	3/240 (2 exencephaly + ablepharia; 1 CP); other observations: nonfused sternebrae + delayed ossification		
Mice: DBA/2J, CD-1, C57 BL, Swiss, i.p. × 4, 8, 10, 12, 14 d, k?, tech.?	Not given	0 (saline)	Not given	—		Giknis and Damjanov, 1980 [27]
	Not given	4 or 6 g/kg of 25% ethanol	Not given	Ocular and renal anomalies in all of the strains	Weight decrease of SW, CD-1 and DBA fetuses	
Mice: C57 BL/6J, i.p. × 1, 7, 8, 9, 10, or 11 d, end point: term tech.?	Not given	0 (saline + starving)	Not given	—		Webster et al, 1980 [28]
	Not given	0.03 ml/g (25% ethanol)	Not given	Absolute numbers not given, 17% exencephaly (treatment d 7); 30% maxillary hypoplasia ± CL ± CP (treatment d 8); anophthalmia; enlargement of brain ventricles	High proportion of resorptions. TM (6 h unconsciousness)	

Mice: C57 BL/6J, i.p. × 2, 7 d, k 14 d, tech. A + F	Not given	0 (vehicle)	Not given	12% eye malformations (microphthalmia, anophthalmia and others). Absolute numbers not given		Sulik et al. 1981 [29]
	Not given	0.015 ml/g (25% ethanol)	72/?	30/72: eye malformations (iris coloboma, microphthalmia, anophthalmia, shortened palpebral fissures); 9 of the 30 had abnormal nasal and lip regions. In addition, 1 exencephaly + 1 anencephaly	Brain size reduced + histological changes of neuroectoderm., TM (lethargy)	
Rat: Sprague-Dawley, diet before conception and throughout pregnancy, end point: term tech. A	24	0 (isocal; some pair-fed)	17/?	–		Tze and Lee, 1975 [30]
	13	30 g/100 ml (water)	5/?	Unspecified number of fetuses with microcephaly + cracked and dry skin	Low litter size + low birth weight	
Rat: Sprague-Dawley, diet × 10, 6–15 d, k 21 d, tech. A ± C + E	21	0 (water)	244/252	2/244: 1 fetus with acandia, clubfoot, ectopic ovaries, shortened trunk + 1 with one rib missing		Schwetz et al. 1978 [26]
	19	10 ml/kg d (15% ethanol)	223/228	0/223: delayed ossification of skull bones + unfused centre of the vertebrae		
Rat: Wistar, diet throughout pregnancy, end point: term, tech. A ± F	49	0 (soya oil, isocal.)	444/?	0/444		Oisund et al. 1978 [31]
	43	7.3 to 11.5 g/kg (total intake)	321/?	2/321: 1 gross malformation of hind part of the body + 1 hydrocephaly		

(continued)

TABLE A-III. Teratological Testing of Ethanol (Continued)

Species, exposure examination	No. of females	Doses used	Survivors/ implants	Malformations/survivors	Other observations (Tm, toxic effects in mothers	Reference
Rat: Long Evans, gavage throughout pregnancy, end point: term, tech. A	74	0 (isocal.; some pair-fed)	770/?	No visible malformations		Abel, 1978 [32]
	25	1 g/kg/d	250/?	No visible malformations		
	21	2 g/kg/d	200/?	No visible malformations		
Rat: Long Evans, gavage × 15, 5–19 d, k 20 d, tech. A	11	0 (isocal. sucrose)	Not given[c]	Not reported		Abel and Greizerstein, 1979 [33]
	15	6 g/kg/d	Not given[d]	Not reported. The study was not designed to detect malformations	Reduced fetal weight. TM[d]	
Rat: Sprague-Dawley, diet before conception and throughout pregnancy, k 20 d, tech. A + C	18	0 (isocal., pair-fed)	179/187	Not reported		Henderson et al, 1979 [34]
	18	0.02 ml/g/d	135/181	Not reported	Reduced organ weight (brain, heart, liver, kidney) + weight loss	
Rat: Sprague-Dawley, gavage twice a day × 3, 11–13 d or 14–16 d, k 20 d, tech. A + C	12 + 15	0 (isocal., pair-fed)	135/139+ 151/151	Not reported		Henderson et al, 1979 [34]
	12 + 15	10 g/kg/d	110/138+ 138/144	Not reported	Reduced organ weight (brain, heart, liver, kidney). TM (severe ataxia)	

Rat: Sprague-Dawley, i.p. × 1, 9 d, cesarean sect. 22 d, tech. A	6	0 (NaCl)	63/63	0.63		Lindenschmidt and Persaud, 1980 [35]
	8	0.02 ml/g/animal	87/99	0/87		
	7	0.02 ml/g/animal[c]	57/58	2/57 (microphthalmia + hydrops fetalis)	TM (2 deaths)	
Rat: Long Evans, diet before conception and throughout pregnancy, k 20 d, tech. A+C±D±E	10	0 (polydipsia)[d]	97/106	0/97		Samson, 1981 [36]
	9	5% ethanol polydipsia	79/89	0/79	Reduced birth weight	
Rat: Long Evans, diet throughout pregnancy, k 20 d, tech. A+C+D+E	9	0 (some pair-fed)	136/142	0/136		Samson, 1981 [36]
	9	5% ethanol (27% EDC)	43/51	0/43		
Guinea pig, diet 3 or 4 times/week, end point: term, tech. A+G	Not given	up to 3 ml/kg/d	Not given	Immaturity of brain at gross examination + cellular lesions, retardation of myelination	TM (sterility, low birth weight, immaturity, stillbirth)	Papara-Nicholson and Telford, 1957 [37]
Rabbit: N.Z., diet × 13, 6–18 d, k 29 d, tech. A±C+E	8	0 (water)	64/72	3/64 (1 spina bifida; 1 anencephaly + ablepharia; 1 fetus with missing spleen)		Schwetz et al, 1978 [26]
	14	3 ml/kg/d	84/126	2/84 (1 CP + protruding tongue + encephalomalacia; 1 bent tail) + minor malformations of carotid arteries		
Piglet: Sinclair S-1, diet before conception and throughout pregnancy, end point: term, tech. A+C	12	0 (pair-fed)	72/80	0/80 (malformations were looked for in stillborn also)		Dexter et al, 1980 [38]
	12	>3 g/kg/d	42/63	4/63 (1 case of each: prolapsed rectum, undescended testicle, hypoplastic testicular tissue, microphthalmia)	Low birth weight: low renal weight	

(continued)

TABLE A-III. Teratological Testing of Ethanol (Continued)

Species, exposure examination	No. of females	Doses used	Survivors/ implants	Malformations/survivors	Other observations (Tm, toxic effects in mothers	Reference
	6	>3 g/kg/d	10/12	4/12 (1 of each: anencephaly, microcephaly, cranial bone hypoplasia, microphthalmia, CP, hypoplasia of extremities, hypodactylia, polydactylia, cryptorchidism, hypoplastic gonadal tissue, cloacal atresia; 2 of each: micrognathia, syndactyly, hypoplasia of tail)	Low birth weight; low renal weight	
Dog: Beagle gavage twice a day throughout pregnancy, end point: term, tech.	10	0 (isocal, sucrose, pair-fed)	51/56	0/51		Ellis and Pick, 1980 [39]
A ± C	28	2.4, 3.0, 3.6, 4.2, 4.7, 5.7 g/kg/d	61/86	3/22 examined (1 renal agenesis + 2 kink tails)	Low birth weight + neonatal mortality, TM (weight loss)	
	Not given	4.2 g/kg/d × 17 d	49/?	15/49: 3 absence of kidney; 4 CP; 7 kink tail; 1 other		

[a] $p < 0.001$ in comparison with controls.
[b] In a further group of ten females receiving 30% EDC (= ethanol-derived calories) in diet no implants occurred.
[c] 1/11 animals failed to carry their pregnancies to day 20.
[d] 10/15 animals failed to carry their pregnancies to day 20.
[e] Corresponding to 0.02 ml/g/day.
[f] Food supplements given to match weight gain of treated animals.
[g] EDC = ethanol-derived calories.

TABLE A-IV. Teratological Testing of Methylmercury (MeHg)

Species, exposure, examination	No. of females	Doses used (mg/kg/d)	Survivors/ implants	Malformations/survivors	Other observations (Tm, toxic effects in mothers)	Reference
MeHg						
Mice: ICR, diet × 1, 10 d, end point: 18 d, tech. A±D±E	20	0 (water)	234/247	7/234 (0 CP; 6 clubfoot; 0/117[a] hydronephrosis; 0/117[a]a absence of sternebrae; 4/117[a] incomplete fusions of sternebrae)[a] fetuses examined		Fuyuta et al. 1970 [40]
	20	10	203/222	16/203 (4 CP; 6/102[a] hydronephrosis; 1/101[a] decreased occipital ossification; 2/101[a] absence of sternebrae; 54/101[a] incomplete fusion) [a] fetuses examined		
	20	15	214/231	68/214 (60 CP; 3/108[a] hydronephrosis; 0/106[a] decreased occipital ossification; 4/106[a] absence of sternebrae; 72/106[a] incomplete fusion)[a] fetuses examined	Low birth weight	
	20	20	215/232	137/215 (126 CP; 20/108[a] hydronephrosis; 6/107[a] decreased occipital ossification; 11/107[a] absence of sternebrae; 82/107[a] incomplete fusion) [a] fetuses examined	Low birth weight	

(continued)

TABLE A-IV. Teratological Testing of Methylmercury (MeHg) (Continued)

Species, exposure, examination	No. of females	Doses used (mg/kg/d)	Survivors/ implants	Malformations/survivors	Other observations (Tm, toxic effects in mothers)	Reference
	20	25	199/226	199/199 (199 CP; 24/101[a] hydronephrosis; 22/98[a] decreased occipital ossification; 20/98[a] absence of sternebrae; 89/98[a] incomplete fusion)	Low birth weight	
MeHg dicyanamide						
Mice 129/SvS1, i.p.	2)	0 (solvent)	92.6%[b]	0		Spyker and Smithberg, 1971 [41]
× 1, 6–13 d, k, 18	2)	2	86.6%[b]	0.5%		
d, tech. C+E	2)	4	83.6%[b]	0.7%		
	[b]	8[c]	83/294	41/83 (including 25 CP; 8 exencephaly; 7 encephalocele; 11 face or limb defects)	TM (16/90 died)	
MeHg dicyanamide						
Mice: A/J, i.p. × 1, 6–13 d, k 18 d, tech.	[d]	0 (solvent)	83.3%	35/132 (3 CP)		Spyker and Smithberg, 1971 [41]
C+E	[d]	2	83%	36/151 (2 CP)		
	[d]	4	86%	72/201 (14 CP)		
	[d]	8	72%	138/227 (91 CP+ 11 micrognathia)	TM (4/36 died)	
MeHg						
Mice: ddN, diet × 1, 6–13 d, end point: 18d, tech. A+C	9	0	79/82	0/79	Developmental retardation	Inouye et al. 1972 [42]
	73[e]	30	413/579	338/413 (231 vaulted cranium; 305 CP; 144 micrognathia; 82 microglossia)		
MeHgCl						
Mice, Swiss, diet × 12, 6-17 d, end point: term, tech. A	17	0 (vehicle)	Not given	0/173		Khera and Tabacova, 1973 [43]
	57	0.001 to 1 (4 levels)	Not given	0/619		

MeHgCl						
Mice: Swiss diet × 12, 6–17 d, fetuses &	23	0 (± vehicle)	Not given	Cerebellar changes: 0/111 examined		Khera and Tabacova, 1973 [43]
2–28 d after birth tech. G	8	0.1	Not given	Cerebellar changes: 0/16 examined		
	13	1.0	Not given	Cerebellar changes: 8/65 examined (histochemistry of CNS)		
MeHgOH						
Mice: C57 BL/6J i.p. × 1, 10 d, k 18 d, tech. C+E	6	0 (solvent)	51/59	0/51		Su and Okita, 1976 [44]
	8	4	56/73	3/56 (1 CP; 1 anophthalmia; 1 micrognathia)	1 TM	
	7	8	25/58	9/25	3 TM	
MeHgOH						
Mice: CD, s.c. or i.v. × 1, 10 d, k 18 d, tech. C+E	15	0 (solvent)	168/194	1/168 (CP)		Su and Okita, 1976 [44]
	10	2[f]	87/105	1/87 (CP)		
	9	4[f]	80/95	1/80 (CP)		
	15	8[f]	162/180	12/162 (10 CP + 2 exencephaly)		
	11	8[g]	106/124	6/106 (CP)		
MeHgOH						
Mice: 129/SvS1, s.c. × 1, 10 d, k 18 d, tech. C+E	5	0 (solvent)	33/36	0/33		Su and Okita, 1976 [44]
	4	8	28/32	0/28		
	9	12	47/?	11/47 (9 CP; 1 facial deformity; 1 skeletal)	1 TM	
MeHgOH						
Mice: 129/SvS1, s.c. × 6, 7–12 d, k 18–19d, tech. C+E	27	0 (solvent)	172/196	0/172		Su and Okita, 1976 [44]
	6	2	39/45	5/39 (CP)		
	21	4	128/163	119/128 (CP)		
	15	5	83/110	81/83 (CP)		
MeHgCl						
Rat: Wistar, diet × 1, 9–11 d, k 18–20 d, tech. G	2	20	16/?	Prominent malformations of the cerebellum with degeneration of nerve cells (incidence not given)		Matsumoto et al. 1967 [45]
			2			
	2	2	20/?	Moderate malformations of the cerebellum (incidence not given)[h]		

(continued)

TABLE A-IV. Teratological Testing of Methylmercury (MeHg) (Continued)

Species, exposure, examination	No. of females	Doses used (mg/kg/d)	Survivors/ implants	Malformations/survivors	Other observations (Tm, toxic effects in mothers)	Reference
MeHg						
Rat: Wistar, diet × 13 or × 8 or × 9, 0-12 d or 7-14 d or 12-20 d, end point: 20 d, tech. A+G	4	0	51/58	0/51		Inouye et al. 1972 [42]
	18[1]	5	185/255	20/185 (17 generalized edema; 2 microphthalmia; 1 shortening of the tail; tissue defects in the neocortex of the brain)	TM	
MeHgCl						
Rat, Charles River, diet × 9, 6-14 d, k 21 d, tech. A ± D ± E ± G[1]	49	0	583/631	Soft tissues: 100/370 examined (82 hydronephrosis, 21 bladder defects, 19 undescended testicles); skeleton: 24/198 examined (6 missing sternebrae)	10 Dead fetuses	Nolen et al. 1972 [46]
	41	0.02	460/486	Soft tissues: 68/230 examined (47 hydronephrosis, 32 bladder defects, 4 undescended testes); skeleton: 32/182 examined (8 missing sternebrae)	6 Dead fetuses	
	36	0.2	384/410	Soft tissues: 84/247 examined (51 hydronephrosis, 37 bladder defects, 7 undescended testes); skeleton: 18/139 examined (5 missing sternebrae)	1 Dead fetus	
	39	4	446/484	Soft tissues: 187/293 examined (118 hydronephrosis, 138 bladder defects, 39 undescended testes); skeleton: 109/160 examined (58 missing sternebrae)	17 dead fetuses, TM (reduced weight gain)	

MeHgOH						
Rat: Charles River, gavage × 14, 6–19 d, k 20 d, tech. A+E	12	0	125/133	20/85 examined with rib abnormalities; 5/40 examined with heart abnormalities		Scharpf et al. 1973 [47]
/	14	1.5	135/141	20/79 examined with rib abnormalities; 0/56 examined with internal abnormalities		
	16	3.0	154/170	6/102 examined with rib abnormalities; 4/52 examined with brain abnormalities; 7/52 examined with heart abnormalities; 10/52 examined with testicular abnormalities	Reduced birth weight	
	16	4.5	108/197	21/73 examined with rib abnormalities; 3/35 examined with brain abnormalities; 15/35 with heart abnormalities; 14/35 examined with testicular abnormalities	Reduced birth weight, TM (6 mothers died)	
	14[k]	6.0	1/108	0/1 rib abnormalities; 1/1 brain and 1/1 heart abnormalities	Reduced birth weight, TM (8 mothers died)	
MeHgCl						
Rat: Wistar, diet throughout pregnancy, k at different times, tech. A ± F	35	0 (corn oil)	Not given	23/167 with eyelid or eye lesions	4/167 Harderian gland lesions	Khera and Tabacova, 1973 [43]
	35	0.002	Not given	25/170 with eyelid or eye lesions	12/170 Harderian gland lesions	
	35	0.01	Not given	35/129 with eyelid or eye lesions	10/129 Harderian gland lesions	

(continued)

TABLE A-IV. Teratological Testing of Methylmercury (MeHg) (Continued)

Species, exposure, examination	No. of females	Doses used (mg/kg/d)	Survivors/ implants	Malformations/survivors	Other observations (Tm, toxic effects in mothers)	Reference
	35	0.05	Not given	28/139 with eyelid or eye lesions	4/139 Harderian gland lesions	
	35	0.25	Not given	51/184 with eyelid or eye lesions	16/184 Harderian gland lesions	
MeHgOH						
Rat Sprague-Dawley, s.c. × 4, 1,5,9,13 d, k 21 d, tech. A→F	41	0 (solvent)	509/513	No gross malformations		Mottet, 1974 [49]
	23	1	283/287	No gross malformations	Cellular necrosis of CNS + running	
	21	"	248/252	No gross malformations	Cellular necrosis of CNS + running, TM (1 mother died)	
	27	"	267/321	No gross malformations	Cellular necrosis of CNS + running, TM (3 mothers died)	
	20	"	118/184	No gross malformations	Cellular necrosis of CNS + running, TM (8 mothers died)	

	10	[illegible]	41/70	No gross malformations	Cellular necrosis of CNS + runting + hydropic fetuses, TM (4 mothers died)	
	20	[illegible]	26/80	No gross malformations	Cellular necrosis of CNS + runting + hydropic fetuses, TM (11 females died)	
MeHgCl						
Rat: Sprague-Dawley, i.p. × 1, 8 d, end point: term. tech.	4	0 (saline)	Not given	No malformations were observed (incidence not given)		Chang and Sprecher, 1976 [50]
A+H	4	4	Not given	No malformations were observed (incidence not given)	At electron microscopy: degenerative changes in the proximal tubules of kidneys	
MeHgCl						
Hamster: Golden, i.p.	41	0 (solvent)	507/563	5/507		Harris et al. 1973 [51]
× 1, 5–10 d, k 15	10	4	116/122	9/116		
d, tech. A+D+E	72	8	384/689	65/384 for a total of 114 malformations including 38 clubfeet, 16 hydrocephalus, 12 micrognathia, 9 cleft palate or lip, 39 others		

(continued)

TABLE A-IV. Teratological Testing of Methylmercury (MeHg) (Continued)

Species, exposure, examination	No. of females	Doses used (mg/kg/d)	Survivors/ implants	Malformations/survivors	Other observations (Tm, oxic effects in mothers)	Reference
MeHgCl						
Hamster: Golden, i.p. × 14, 1–14 d, k 15 d, tech. A+D+E	5	0 (solvent)	54/63	Not reported		Harris et al. 1973 [51]
	10	2	69/112	25/69 for a total of 30 malformations including 11 clubfeet, 5 hydrocephalus, 14 others	TM (2 mothers died)	
MeHgCl						
Cat: Persian and European, diet × 49, 10–58 d, k 59 d, tech. C+E+F	7	0 (solvent)	20/24	1/20 (skeletal)	0/17 cerebellar histological changes	Kheta, 1973 [48]
	5	0.03	35/40	2/35 (1 skeletal + 1 spina bifida)	0/7 cerebellar histological changes; reduced birth weight	
	6	0.083	22/28	3/22 (2 skeletal + 1 umbilical hernia)	1/14 cerebellar histological changes; reduced birth weight	
	13	0.25	51/97	11/51[a] (9 skeletal + exencephaly + 1 umbilical hernia)	9/17 cerebellar histological changes; reduced birth weight	

MeHgCl						
Miniature Swine, diet before pregnancy?, k 109 d, tech. A+E	20	0	114/114	0/114		Earl et al. 1973 [52]
	30	0.05 to 0.5	717/96	0/71	TM	
MeHgCl						
Dog: beagle, diet throughout pregnancy, k 60 d, tech. A+E	39	0	169/178	2/169 (1 CL + shortened tail; 1 microphthalmia)		Earl et al. 1973 [52]
	51	0.1 to 0.25	138/140	2/50 in the 0.1 mg/kg/d group (1 CP + enlarged umbilical opening + enlarged fontanelle; 1 enlarged umbilical opening)	TM (stillbirth)	

[a]The figure refers to the number of fetuses examined.
[b]Absolute figures per group not given. The whole series included 214 litters and 1,391 implants.
[c]k 15 d.
[d]Absolute figures not given per group. The whole series included 96 litters and 889 implants.
[e]Eight groups of females treated in different days.
[f]s.c.
[g]i.v.
[h]No control group; lesions were much less severe in animals concurrently given penicillamine.
[i]Three groups of females treated in different periods.
[j]In this experiment, each group of rats (including controls) was divided into three subgroups concurrently treated with 0, 0.1 and 20 mg/kg/d trisodium nitrilotriacetate; however there was significant change due to the presence of NTA.
[k]In a further group treated with 8.0 mg/kg/d 21/21 females died.
[l]Dose unspecified; maternal liver concentration < 15 μg/g Hg; range of the total dose 2–16 mg/rat.
[m]sl; maternal liver concentration 15–25 μg/g.
[n]id; maternal liver concentration 25–50 μg/g.
[o]id; maternal liver concentration 50–75 μg/g.
[p]id; maternal liver concentration 75–99 μg/g.
[q]id; maternal liver concentration > 99 μg/g.
[r]It is unclear whether fetuses examined were 51 or 34.

TABLE A-V. Teratological Testing of PCBs

Compound· species, exposure, examination	No. of females	Doses used (mg/kg/d)	Survivors/ implants	Malformations/survivors	Other observations (Tin. toxic effects in mothers)	Reference
Clophen A 60						
Mice: NMRI. oral × 62. females 62 d preconceptionally, k 8-10 d. tech. A	11	0	250 (87%) implantations	-	PCB decreased implantations and extended estrous cycles	Örberg and Kihlström, 1973 [53]
	14	0.025	249 (79.5%) implantations	—		
2,2'-diCB						
Mice: NMRI. oral × 3. 1-3 d. tech. A	37	0	—	—	Dams with litter, and litter size decreased, length of pregnancy increased in the treated groups	Török, 1976 [54]
	18	375	—	—		
	38	750	—	—		
2,4',5-triCB						
Mice. NMRI, oral × 7, 1-7 d, k 7 d, . tech. A	56	0	418 (92.3%) implantations	—	PCB decreased implantations	Örberg, 1978 [55]
	20	0.05	152 (92.7%) implantations	—		
	40	0.5	296 (87.8%) implantations	—		
2,2',4,4',5,5'-hexaCB						
Mice· NMRI, oral × 7, 1-7 d, k 7 d, tech. A	56	0	418 (92.3%) implantations	—	PCB decreased implantations	Örberg, 1978 [55]
	20	0.05	154 (94.5%) implantations	—		
	32	0.5	238 (83.8%) implantations	—		

3,3'4,4'5,5'-hexaCB						
Mice: CD-1, gavage × 10, 6–15 d, k 18 d, tech. A?	—	0 (vehicle)	—	Absolute numbers not given. Average percentage malformed fetuses/litter 0.9%[a]		Staples et al. 1980b [56]
	—	2	—	Absolute numbers not given. Average percentage malformed fetuses/litter 11.7%[a]		
	—	4	—	Absolute numbers not given. Average percentage malformed fetuses/litter 3.6%[a]		
	—	8	—	Absolute numbers not given. Average percentage malformed fetuses/litter 65.5%[a]	TM	
	—	16	—	Absolute numbers not given. Average percentage malformed fetuses/litter 60.6%[a]	TM	
Arochlor 1254						
Rat: Wistar, gavage × 10, 6–15 d, k 22 d, tech. A + E	9	0 (solvent)	93/96	17% with skeletal anomalies and 47% with visceral anomalies (absolute numbers not given)		Villeneuve et al. 1971 [57]
	10	6.25	107/119	10% with skeletal anomalies and 17% with visceral anomalies (absolute numbers not given)		
	10	12.5	113/117	8% with skeletal malformations and 24% with visceral malformations (absolute numbers not given)		

(continued)

TABLE A-V. Teratological Testing of PCBs (Continued)

Compound - species, exposure, examination	No. of females	Doses used (mg/kg/d)	Survivors/ implants	Malformations/survivors	Other observations (Tm, toxic effects in mothers)	Reference
	10	25	114/121	9% with skeletal malformations and 15% with visceral malformations (absolute numbers not given)		
	9	50	103/107	9% with skeletal malformations and 28% with visceral malformations (absolute numbers not given)		
	7	100	84/89	15% with skeletal malformations and 0% with visceral malformations (absolute numbers not given)		
Arochlor 1254						
Rat, Sherman,[b] gavage × 9, 7–15 d, end point: weaning, tech. A	19	0 (solvent)	230/?	0/230	227 weaned	Linder et al, 1974 [58]
	9	10	109/?	0/109	108 weaned	
	10	50	134?	0/134	127 weaned, low birth weight	
	9	100	91/?	0/91	8 stillbirths, 25 weaned, low birth weight	
Arochlor 1254						
Rat: Sherman,[b] gavage × 9, 7–15 d, end point: weaning, tech. A	12	0 (solvent)	148/?	0/148	4 stillbirths, 138 weaned	Linder et al, 1974 [58]
	12	100	150/?	0/150	10 stillbirths, 124 weaned	

Arochlor 1254						
Rabbit, gavage × 28, 1–28 d/k 29 d, tech. A	16	0 (solvent)	126/127	0/126		Villeneuve et al. 1971 [57]
	3	1	18/19	0.18		
	4	10	27/27	0/27	Increased liver weight	
	2	12.5	2/15	0/2	Cephalic subcutaneous hemorrhages and asymmetric skull in 2 of 5 dead fetuses, increased liver weight	
	8	25	35/72	0/35	Increased liver weight	
	3	50	0/21	—	TM (2/3 died before term)	
	4	25[c]	235/37	0/25	Increased liver weight	
Arochlor 1248						
Monkey: Rhesus, diet before conception and throughout pregnancy, end point: term, tech. A	12	0	12/12	0/12		Barsotti et al. 1976 [59]
	14	2.5 or 5 ppm in diet	6/14	0/6	7 abortions + 1 stillbirth, small size of newborns	
Arochlor 1248						
Monkey: Rhesus, diet before pregnancy, end point: term + 4 postnatal months[d], tech. A+F	8	0	8/8	0/8		Allen et al. 1980 [60]
	15	2.5 or 5 ppm in diet	7/15	0/7 (hyperpigmentation of skin; hyperplastic gastritis and keratinization of face hair follicles occurred in 2 dead infants)	3 abortions	

[a]Predominant malformations are reported to be CP and hydronephrosis.
[b]These experiments were a part of a large series of studies on the effects of PCBs on rat reproduction, including microscopic examination of the liver in two generations. Both Aroclor 1254 and 1260 fed 5 ppm in the diet induced liver changes both in F_1 and F_2 weanlings of either sex (1 ppm for F_1 males fed Aroclor 1254). Liver changes included enlarged hepatocytes, cytoplasmic inclusions, foamy cytoplasm, pigment, fibrous strands, adenofibrosis, and nodules.
[c]×22 (7–28 d).
[d]Therefore both transplacental and breast-fed exposure occurred.

APPENDIX A REFERENCES*

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*Appendix references are preceded by an "A" in the first part of this paper.

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